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PERSONALITY CHANGES ACCOMPANYING CEREBRAL LESIONS

I. RORSCHACH STUDIES OF PATIENTS WITH CEREBRAL TUMORS

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GENERAL STATEMENT OF THE PROBLEM

The purpose of this study has been twofold. The Rorschach method of evaluating "personality structure" was used in some hundred cases at the Montreal Neurological Institute; first, to test its efficacy as a tool in answering questions of both clinical and psychologic interest, and, second, to throw light on the term "organic personality structure" as used in the Rorschach literature. Since these two problems require somewhat different introductions, they may be considered separately.

THE RORSCHACH METHOD AS A TOOL IN CLINICAL PSYCHOLOGY

Mention may be made briefly of five questions to which an answer from the psychologic angle may be of value clinically. Despite an ever growing body of literature dealing with the psychologic status of patients with lesions of the brain, there is still considerable difference of opinion as to whether psychic changes are the inevitable accompaniment of lesions of the brain and removal of brain tissue. As has been pointed out by me in a recent publication,[1] one finds reported in the literature cases of marked mental changes side by side with those in which a lack of psychologic disturbance was noted. Rylander,[2] in considering the reports of cases in which one frontal lobe had been removed, also called attention to this contradiction. He said: "Euphoria and depression, distractibility and lack of distractibility, hypokinesia and

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1. Harrower-Erickson, M. R., in Whipple, G. M.: Thirty-Ninth Yearbook of the National Society for the Study of Education, 1940, pt. 1.

2. Rylander, G.: Personality Changes After Operation on the Frontal Lobes: A Clinical Study of Thirty-Two Cases, London, Oxford University Press, 1939.

hyperkinesia, *intact intellectual functions and injured intellectual functions* are some of the apparent contradictions described." [3]

One may therefore consider the following questions:

1. Assuming that after removal of a large amount of tissue the patient still appears superficially normal, making a creditable showing on both intelligence and performance tests, will the Rorschach method nevertheless bring to light a "changed" personality—that is, one sufficiently different from the normal and sufficiently consistent among patients with lesions of the brain to be considered a reliable indication of a change resulting from the organic condition? (Granted that there is such a change, the questions whether it arose because of the presence of pathologic tissue or because of the absence of brain tissue, whether the location of the lesion was influential, etc., must be further studied.)

2. Assuming that there can be found a record typical of, or reflecting, severe damage to the brain, is it sufficiently reliable to allow a differential diagnosis in cases in which the causation of the disease is questioned? Can the Rorschach method, for example, give an answer, independent of all clinical data, to the questions: "Is this condition due to a tumor of the brain or to hysteria? Or is the patient a psychologically normal person suffering intense headache from noncerebral causes?"

3. Can the Rorschach test differentiate between "genuine" and focal epilepsy? How do the records of epileptic patients differ from those of normal persons and from those of patients with tumor of the brain? Can a change be found following the removal of scar tissue from the brain of a patient with traumatic epilepsy? Does improvement in the record of such a patient relate to the cessation of attacks, or to the presence or absence of abnormal waves as indicated by the electroencephalogram?

4. Can the Rorschach method, despite the fact that it normally involves language, be adapted for use in cases of aphasia so that light can be thrown on the personality structure and intelligence of patients with aphasia despite the disturbance in language?

5. In post-traumatic conditions, can mental changes due to trauma of the brain be distinguished from malingering or from neurotic anxiety?

Any one method or procedure giving answers, even in part, to such questions [4] would seem to justify its use in a clinical situation.

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3. Dandy, Rowe, Jefferson, Clovis Vincent and Hebb have called attention to the lack of psychologic disturbance following removal of brain tissue. Among the numerous writers who have stressed the presence of some specific defect are Goldstein, Baruk, Frazier, Brickner, Strauss and Keschner.

4. The last three questions will be dealt with in separate publications.

THE TERM "ORGANIC PERSONALITY" [5] IN THE RORSCHACH LITERATURE

A brief survey of the use of the Rorschach method in the study of patients with cerebral lesions will show, I think, that the term "organic personality" needs more careful definition than has yet been afforded it.

In the original monograph,[6] Rorschach's "organic cases" are perhaps the least convincing and the most incomplete. He gave as examples of "organic" psychosis 1 case of "depression with arteriosclerotic dementia," 1 of Korsakoff's psychosis, 1 of dementia paralytica, 1 of senile dementia and 1 of encephalitis lethargica. But, as Piotrowski [7] commented:

> Rorschach did not present his ideas about the organic personality in a systematic manner. He had not examined all types of organic nervous disorders, for example brain tumours or brain concussions, so that his conclusions regarding organic cases were not applicable to all organic patients.

Oberholzer,[8] who developed the Rorschach method for use in cases of cerebral injury, distinguished between an "organic condition" and a "superimposed neurosis" in 1 case and, in a recent paper, read at a meeting of the American Psychiatric Association, discussed the posttraumatic conditions. The records in the latter instance, however, were not reported in detail, nor was the extent of the traumas or their location discussed. Beck,[9] in his admirable monograph, admitted the absence of data on patients with cerebral lesions in his material and emphasized the need for work along these lines.

Klopfer and Tallman [10] have studied Brickner's famous patient, Mr. A., on whom bilateral frontal lobectomy was done. These postoperative studies, made on three successive occasions, showed an interesting parallel between the Rorschach records and the patient's behavior. There are, however, no similar studies of patients after removal of tissue in different areas of the brain which might make possible an answer to the questions whether it was the frontal or the bilateral aspect of the

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5. This term is quoted with the full realization that it is an example of medical slang.

6. Rorschach, H.: Psychodiagnostik, ed. 2, Bern, Hans Huber, 1932.

7. Piotrowski, Z.: The Rorschach Inkblot Method in Organic Disturbances of the Central Nervous System, J. Nerv. & Ment. Dis. **86**:525-537, 1937.

8. Oberholzer, E.: Rorschach's experiment in Traumatic Mental Disorders, read at the annual meeting of the American Psychiatric Association, Chicago, May 8-11, 1939; Zur Differentialdiagnose psychischer Folgezustände nach Schädeltraumen mittels des Rorschachschen Formdeutversuchs, Ztschr. f. d. ges. Neurol. u. Psychiat. **136**:596-629, 1931.

9. Beck, S. J.: Introduction to the Rorschach Method: A Manual of Personality Study, with Preface by F. L. Wells, Monograph 1, American Orthopsychiatric Association, Menasha, Wis., George Banta Publishing Company, 1937.

10. Klopfer, B., and Tallman, G.: Rorschach Study of a Bilateral Lobectomy Case, Rorschach Research Exchange **1**:77-88, 1937; **3**:31-36, 1938.

operation which resulted in the type of Rorschach record given and whether it was the fact that an area of brain had been removed or the presence of pathologic tissue which was responsible for the symptoms.

Another important study is that of Piotrowski [7] on "18 cases with involvement of the brain, 10 cases with noncerebral disturbances of the central nervous system, and 5 cases of conversion hysteria." As a result of comparison of these cases, Piotrowski postulated ten signs which might be considered indicative of a cerebral lesion. He stated that when six or more signs are present in a given record, the presence of damage to cerebral tissue is strongly suggested. However, the location, the type of lesion and the status (preoperative or postoperative) of the patients in Piotrowski's 18 cases of cerebral involvement are not mentioned. There is also some difficulty when this study is compared with that of Nadel.[11] Nadel used Piotrowski's ten signs as his criteria for differentiating between patients with involvement of the frontal lobes and a control group of patients from the same hospital, of whom 5 had tumors in other areas of the brain.[12] According to the records of Nadel, these 5 control subjects all showed fewer than the six signs regarded as the hallmark of an abnormal or typically "organic" Rorschach record. Two showed three such signs, 2 only one sign and 1 no signs. In Piotrowski's group of patients with cerebral disease, however, of the 18 subjects tested all showed over four signs, and 17 showed five signs and over. Since it is unlikely that this group of 18 patients all had involvement of the frontal lobes, one is faced with alternative answers: Piotrowski used the Rorschach method to show the abnormality of the records of all patients with cerebral lesions regardless of the location of the lesion, and Nadel used it to show the essential normality of the records of patients with lesions in areas other than the frontal lobes, as contrasted with the abnormality indicated by the records of those with lesions of the frontal lobes.

Thus, in addition to the five general questions already mentioned, this investigation aimed at collecting records from patients with cerebral lesions of different types, of different duration and in different locations. I was interested in comparing the preoperative and postoperative records of the patients, both as a group and individually. I was interested in

11. Nadel, A.: A Qualitative Analysis of Behavior Following Cerebral Lesions Diagnosed as Primarily Affecting the Frontal Lobes, Arch. Psychol., 1938, no. 224.

12. The conditions of the other 10 control subjects used in this study were diagnosed as follows: muscular dystrophy, tumor of the cauda equina, idiopathic epilepsy, multiple sclerosis of the cervical part of the spine (2 cases), hemiatrophy, neurosyphilis involving the cerebellum, psychoneurosis (2 cases) and poliomyelitis.

the comparison of the records of patients with clean and with partial removal of brain tissue and those of patients with discrete and with infiltrating lesions.

METHOD OF PRESENTATION OF RESULTS: THE NORMAL PSYCHOGRAM

A detailed description of the Rorschach method is unnecessary in view of the many excellent articles describing its procedure, scoring and interpretation.[13] In using a graphic method of tabulating the results, I have aimed at making the necessary comparison between patients and normal controls more easily available to those with only a general familiarity with the Rorschach procedure. The subject's responses to the 10 ink blot pictures, therefore, have been tabulated so that the output, the type of mental approach and the span of psychic reactivity, or richness of psychic experience, can be easily seen. These diagrammatic representations of the determinants of the responses constitute a bird's eye view of some of the main features of the record but can by no means be considered a full interpretation. Many aspects of the record are not amenable to treatment in this way, and no record can be judged on the basis of such representation alone.[14] However, when gross differences in records can be seen even by such a method, one is justified in using it to cover as much ground as possible.

The question of what can be considered a normal record, which may be used as a basis of comparison, is more difficult with the Rorschach test than with most tests. Persons may be normal, healthy, well balanced and intelligent and yet give Rorschach records which differ widely. Again, there may be the well balanced person on the "average" level and the well balanced person on a far more sophisticated intellectual plane. A thousand persons might have an intelligence quotient of 135, for example, but each Rorschach record would be different. Again, while it is not difficult for the experienced Rorschach examiner to pick out a normal record from a group of abnormal ones, or vice versa, it constitutes a problem when one wishes to present records in a concise fashion and have the salient abnormal features stand out in contradistinction to an established norm.

For this study I have given as standards of comparison one hypothetic normal record and two composite pictures drawn from two different groups: a well trained, above average group of "scientists" and an "average" group of hospital employees.[15] In a composite picture of this kind, in which the average scores for all the types of responses are charted, one can expect only certain "group" characteristics to come to light. Moreover, there is the danger that certain

13. Booth, G. C.: Objective Technics in Personality Testing, Arch. Neurol. & Psychiat. **42**:514-530 (Sept.) 1939. Klopfer, B.: The Technique of the Rorschach Performance, Rorschach Research Exchange **2**:1-15, 1938; Theory and Technique of Rorschach Interpretation, ibid. **3**:152-194, 1939. Monnier, M.: Le test psychologique de Rorschach, Encéphale **29**:189-201 and 247-270, 1934. Rorschach.[6] Beck.[9]

14. It is planned to publish separately the records of particularly important cases, with discussion in greater detail, in the Rorschach Research Exchange.

15. If the scores in these groups are compared with similar averages found for groups of "superior" and "average" persons by other investigators (Davidson, H., and Klopfer, B.: Rorschach Statistics: I. Mentally Retarded, Normal, and Superior Adults, Rorschach Research Exchange **2**:164-169, 1938), they will be found to be in close agreement, despite slight differences in the technic of scoring.

individual records will unduly distort the total picture. But since one expects from the method a great variety in individual records, one may also expect any composite, or group, picture to be made up of records which differ greatly in certain ways. Although it is anticipating the results, I may say here that one of the most striking differences shown by a comparison of records of normal persons

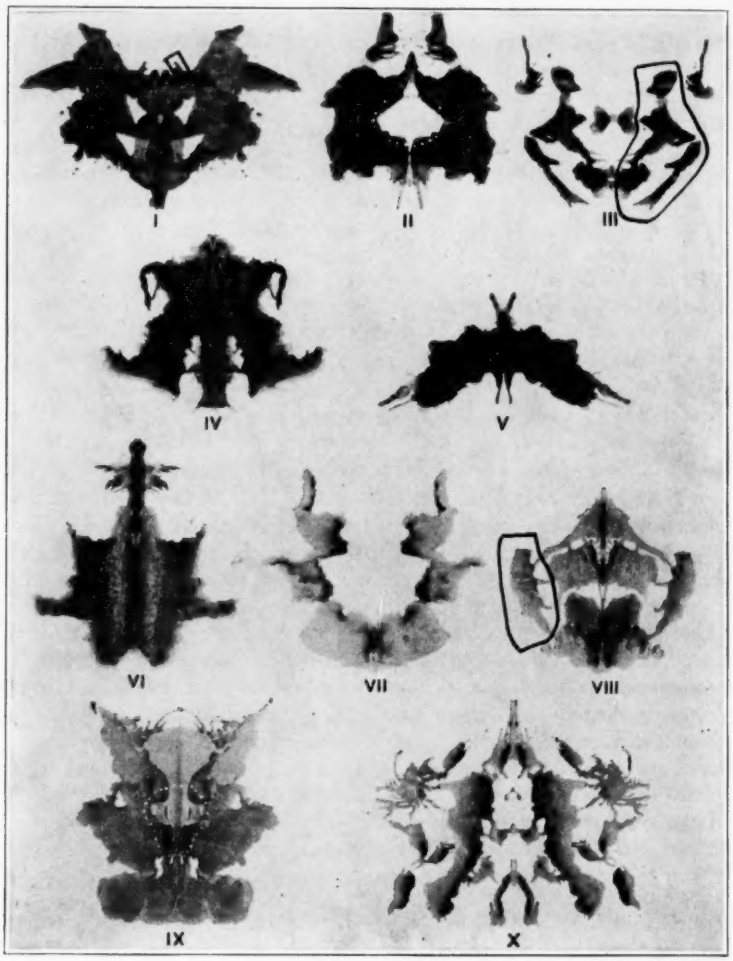

Fig. 1.—The ten ink blot pictures composing the Rorschach test material.

and records of patients with tumor is the similarity and uniformity of the individual psychograms which go to make up the composite picture of the pathologic group and the individuality of each normal psychogram.

The hypothetic record of a normal person is given to illustrate certain relationships in the scores which epitomize a well balanced personality and to explain briefly the type of response denoted by the letters at the bottom of each psychogram. If figure 1 (an uncolored and reduced reproduction of the Rorschach

cards) and figure 2 (the record of the hypothetic normal person) are compared, the transition between actual response and scoring may be illustrated.

Explanation of Figure 2 in Terms of Figure 1.—R stands for the total number of responses given to the series of ten ink blots. Thirty responses are given in the record in figure 2. All other records are drawn to the same scale.

Location of Responses: *W* stands for the number of "whole" answers given (the number of times the whole card was used in the interpretation). Example: card V seen as a bat or a butterfly.

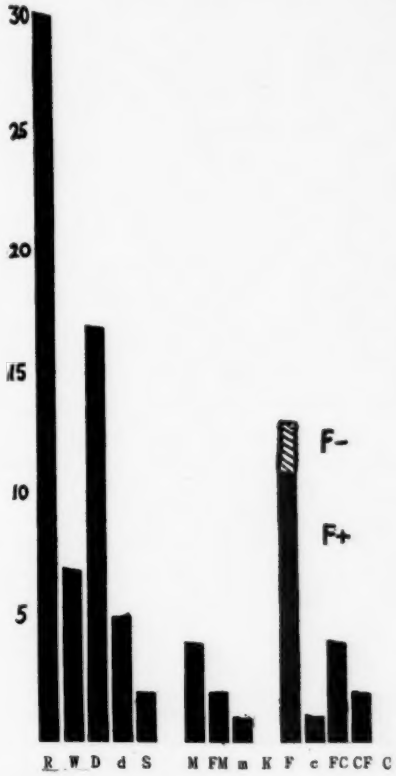

Fig. 2.—Record of a hypothetic normal person, showing the following ratios: $W:D:d:S$; $M:FM:m$; $FC:CF:C$; F plus; F minus; $R:F$; $W:M$, and $M:\Sigma C$. (See text for explanation.)

D stands for an "obvious," or large, detail. Example: the area marked off in card VIII seen as "some animal." *d* stands for a small detail. Example: the small area marked off in card I seen as a hand in a mitten.

S stands for the white space. Example: the enclosed space in card II seen as a top.

Determinants of Responses: *M* stands for human movement. Example: two men bowing to each other in card III.

FM stands for animal movement. Example: the "bat flying" in card V.

m stands for movement of inanimate objects or for expression. Example: a face with an "evil expression" seen in card IX.

K stands for shading used as diffusion. Example: card VII seen as clouds.

F stands for form and may be good or bad, or plus or minus, according to the validity of the representation. (In my charts the cross hatched areas represent the *F* minus answers.) Examples: card V seen by many persons as a bat (*F* plus) or the same card seen as "my neck and breasts" (*F* minus).

c stands for shading used as texture or surface quality. Example: card IV seen as a pelt or skin.

FC, *CF* and *C* stand for responses in which color plays an increasing role. Since the reproduction is not colored, these cannot be illustrated. *FC*, however, represents answers in which the correct form and appropriate coloring are used; *CF*, a response in which color is the determining factor and form subsidiary, and *C*, a response in which color alone is the determining factor.

From figure 2, the record of the hypothetic normal person, six ratios will be noted, which are important milestones in consideration of a record. These are:

1. The relation of *W* : *D* : *d* : *S*, or the number of times that the whole card, a large detail, a small detail or the white space is chosen for interpretation. In a normal record one may expect from 20 to 30 per cent *W* responses, 45 to 55 per cent *D* responses, 10 to 20 per cent *d* responses and less than 10 per cent *S* responses. However, this indication of mental approach can vary greatly from person to person. An increase in the *W* answers will mean, in a good record, a predominantly abstract or theoretic approach. However, when the *W* responses are *F* minus ones, that is, poorly perceived forms, then a proportionally high percentage of *W* responses means something very different, because a series of vague, unjustified whole responses, such as "part of my body," given indiscriminately to the ten cards epitomizes not an abstract approach to theoretic problems but rather the least developed type of intellectual capacity or the most deteriorated intelligence. Emphasis on, or a higher percentage of, *D* responses indicates an essentially practical outlook. Preoccupation with the small details (*d*) means an emphasis on detail, a critical outlook. A high percentage of *S* responses may indicate a negative attitude toward the world or oneself.

2. In the ratio of *M* : *FM* : *m*, the *M*, or human movement, responses should be more numerous than the *FM* (animal movement) responses, and both should outweigh the *m* (movement of inanimate objects and expression) responses. This means that the integrated, creative activity (*M*) of the person tested is stronger than the more primitive drives (*FM*) and that both are allowed freer play in the person's makeup than are the repressive tendencies (*m*).

3. In the same way, the well integrated and well adjusted emotional responsiveness (*FC*) should outweigh the more primitive egocentric emotions (*CF*), and both should be more numerous than the purely explosive, uncontrolled emotionality evidenced in *C*. (In this hypothetic normal subject *C* is 0.) When *FC*, *CF* and *C* are considered together, the symbol ΣC is used.

4. The *F* column, exemplifying as it does controlled intellectual responses, should not constitute more than 50 per cent of the entire number of responses. If it is developed at the expense of all other types of reactions it means a constricted personality in which spontaneity, creativeness and emotional expression and sensitivity are lacking or inhibited.

5. The *F* column should contain at least 75 per cent of good form responses. The intelligent normal subject will usually give more than this.

6. The $M : \Sigma C$ ratio epitomizes what Rorschach described as the *Erlebnistypus*, the relation of the inner life to the emotional, social or external responses. According to Rorschach, the introvert is the person (with *M* greater than ΣC) who fulfils himself through drawing on his inner resources. The extrovert (with ΣC greater than *M*) is, according to Rorschach, the person who needs others for his own development, who finds himself in his contacts with others. The "ambi-equal" personality type (with *M* equal to ΣC) develops along both these lines, using each type of experience to enrich the other.

In scoring this relation, each *M* (human movement) response counts as 1. The color responses are scored according to the extent to which color dominates (*FC*, 0.5; *CF*, 1; *C*, 1.5). My hypothetic normal subject in this case is of the ambiequal type; his 4 *M* responses are balanced by 4 *FC* and 2 *CF* responses; the $M : \Sigma C$ ratio, therefore is 4 : 4.

In the hypothetic record there are two columns the significance of which has yet to be mentioned. There are the *c* column (shading used as texture [fur; rug]) and the *K* column (shading used as diffusion [clouds; smoke]). In general, the presence of *c* in a record, when not disproportionately emphasized, means receptiveness toward the external world and toward others, sensitivity and tact. The same characteristic, however, in certain settings may mean oversensitiveness, apprehension or, in still other constellations, undue preoccupation with sensuous sensation. The *K* responses signify anxiety of a rather vague, undifferentiated type. My hypothetic normal subject indicates by his answers that he is sensitive but is not unduly anxious.

In order to simplify the results, I have not included on the base line several other determinants of which Rorschach workers make use. The chief of these is *FK*, which is indicative sometimes of self consciousness and at other times of introspective ability to grapple with one's own problems.

It should be pointed out again, as it constantly is by those who are familiar with the Rorschach method, that no one type of response invariably means a given type of reaction in the subject. The record must be considered in its entirety. This oversimplified discussion of a hypothetic case, however, is given in the hope that the differences between my "abnormal" records and those which I derived from normal subjects will stand out more clearly.

COMMENT ON THE COMPOSITE PICTURE OF SUPERIOR AND AVERAGE NORMAL SUBJECTS

When one compares the superior and the average group (fig. 3 *A* and *B*) as to their composite pictures one finds several differences which are not surprising.[9] The output in the superior group is somewhat higher (*R*, 38 and *R*, 25). The relation of $W : D : d$ is shifted for the superior group toward emphasis on the *W*, the theoretic or abstract rather than the practical approach. The *M* responses are more numerous; i. e., the creative and satisfactorily integrated inner life is richer. The emotional responses are more numerous, and the relation between

the more integrated and the more primitive is better (in *A*, *FC* is greater than *CF*; in *B*, *CF* is greater than *FC*). The relation of good form to poor form shows the superior mental ability in the "scientist" group. Such composite pictures, however, must be seen side by side with some of the records which compose them. Figure 4 shows two very different personalities in the scientist group; figure 5 shows some of the different

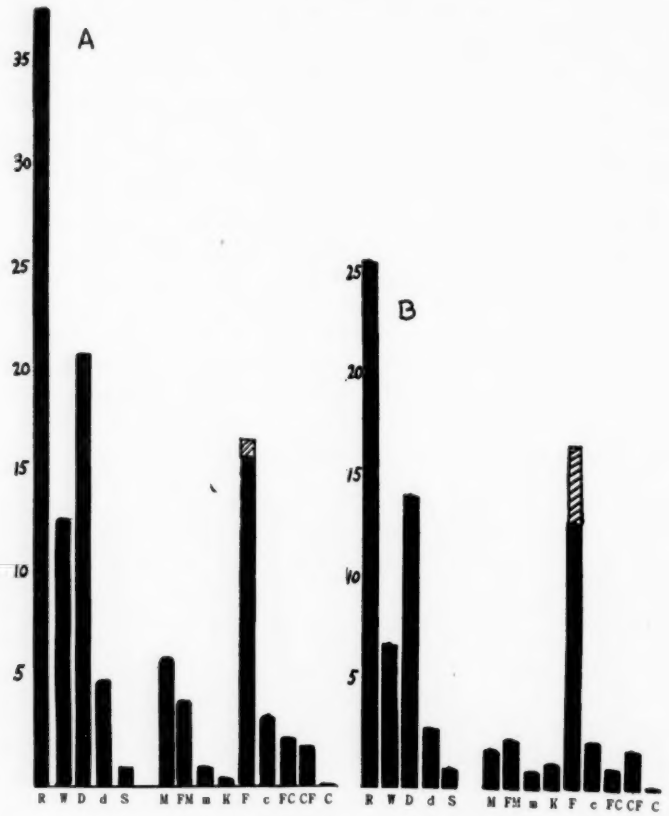

Fig. 3.—*A*, composite record of 10 scientists; *B*, composite record of 10 hospital employees.

types among the average group. Since I am not really concerned with the discussion of normal records, I shall point here only to the most striking differences. Figure 4 *A*, for example, is almost the reverse of figure 4 *B*, while figures 5 *C* and 5 *D*, from the employee group, represent widely divergent personality types. From a study of these composite and individual pictures it is hoped that a basis of comparison will be possible for the records which follow.

PATIENTS WITH TUMOR OF THE BRAIN

The patients who are now to be discussed may be divided into two groups: (1) those with verified tumor and (2) those suspected of having tumor.

Patients with Verified Tumor.—This group, consisting of 25 patients, is considered here; the group of patients suspected of having tumor is

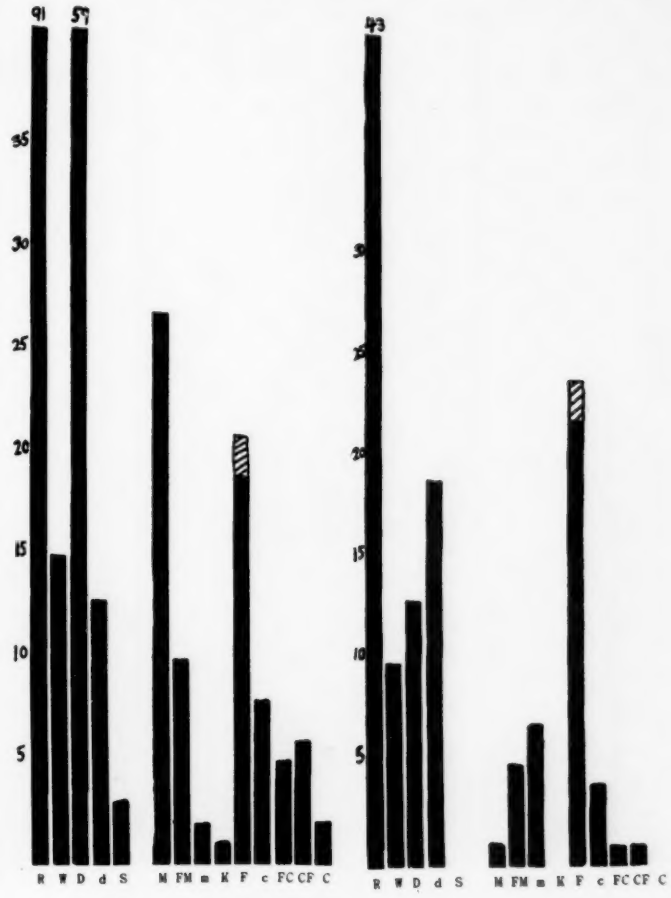

Fig. 4.—Individual record of each of 2 scientists.

discussed in the section on differential diagnosis (page 883). Since 3 patients of this group were examined both before and after operation the number of records discussed is 28. These 28 records have been considered from three aspects:

A. Comparison of Preoperative and Postoperative Records: Ten preoperative and 18 postoperative records are considered.

Throughout the records there is a larger number of postoperative than of preoperative studies. The reason for this is that frequently preoperative conditions lead to an emergency, and even if the condition is not extremely acute the patient is often drowsy or under medication for severe headache. Since I did not wish this factor to obscure the more fundamental personality picture, I was careful to choose for con-

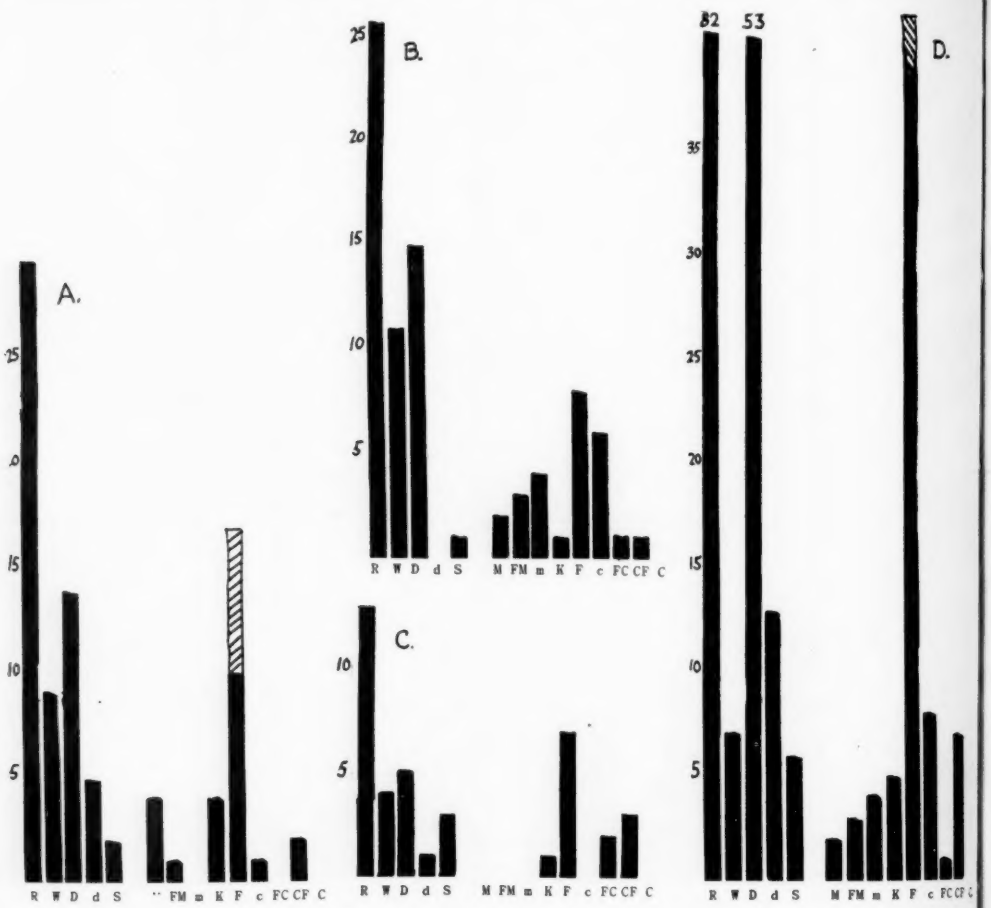

Fig. 5.—Individual record of each of 4 hospital employees.

sideration only cases in which the patient was able to cooperate easily. An exception was made in 1 case, in which a preoperative record was taken under poor physical conditions, but that will be discussed separately. (fig. 17). The reason that (with the exceptions mentioned) different patients were chosen for study before and after operation is twofold. It seemed well to include as many different personalities as

possible in this group, so that if any group characteristics should be evidenced they would emerge from different ages, backgrounds and sexes. Since, for various reasons, it is more difficult to follow the same patient preoperatively and postoperatively, a study exclusively along these lines would have been more limited in its scope.[16] An even more important reason, however, is that patients, whether examined preoperatively or postoperatively, should see the cards for the first time when they make the records under consideration. In the event of postoperative improvement one would be open to the criticism that, since this was the second time the test had been taken, the improvement might

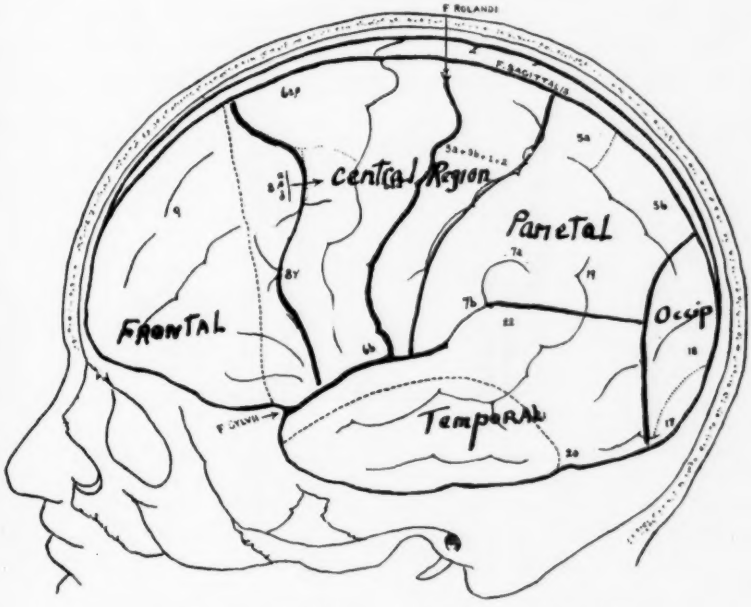

Fig. 6.—Locations of tumors observed in this series.

be due to practice. Although no one who has worked extensively with the Rorschach test believes that this is the case, it seemed well to avoid any possible extraneous influence. Fifteen of the 18 postoperative records, therefore, were given by patients taking the test for the first time; the other 3 are included for reasons which will be shown later.

16. Rylander [2] found a similar difficulty confronting him in his initial attempt to study patients before operation. He said (page 42): "Despite the fact that brain tumours are now diagnosed at an earlier stage than previously, acutely ill patients lying in a neurosurgical ward awaiting a brain operation are poor subjects for psychological examination. They are often tired and sensitive, generally suffering from headache and dizziness, and furthermore their sight is not infrequently impaired."

B. Type of Lesion: Ten records were obtained from patients with rapidly growing tumors (glioblastomas and carcinomas). Eighteen were obtained from patients with slowly growing tumors, including diffuse astrocytomas, meningeal fibroblastomas, oligodendrogliomas and cystic astrocytomas. Of the first group, 3 were obtained preoperatively and 7 postoperatively; of the second, 7 were obtained preoperatively and 11 postoperatively.

C. Location of Lesion: All areas were represented, in the following proportions:

Frontal region: 9 records, 4 preoperative and 5 postoperative.
Parietal region: 4 records, 3 preoperative and 1 postoperative.
Temporal region: 10 records, 2 preoperative and 8 postoperative.
Occipital region: 5 records, 1 preoperative and 4 postoperative.

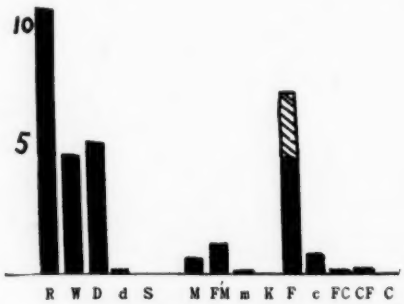

Fig. 7.—Composite record of 25 patients with tumors of the brain, variously located. The tests were made preoperatively in some instances and postoperatively in others. In 3 cases both preoperative and postoperative tests were given the same patient. The number of records included in the composite chart, therefore, is 28.

Figure 6 illustrates the areas included by the various terms and shows how the location of the lesion was recorded from the operative notes of the surgeons in all cases.

Figures 7 to 14 illustrate the various subgroupings in a composite manner. Figures 15, 16, 17 and 18 give individual records.

PSYCHOGRAMS OF PATIENTS WITH TUMORS OF THE BRAIN

If, ignoring the scientists as a specialized group, one takes as a standard of comparison figure 2, the record of the hypothetic normal person, and figure 3 *B*, the composite record of the 10 hospital employees, it can be seen at a glance that the records epitomized in figures 7 to 18 differ markedly from the norms and have certain group characteristics. The 28 records which comprise figure 7 show: (1) a poorer output (50 per cent less); (2) a *W: D: d: s* proportion too heavily weighted on the *W*, i. e., without an adequate number of clearly perceived forms;

(3) a percentage of *F* responses higher than normal; (4) a poorer range of psychic reactivity, i.e., a more constricted and uniform personality structure ($M : \Sigma C$ barely 1 : 1), and (5) absence of *K* and *FK* throughout.

As has been mentioned on page 867, *FK* does not appear on the base line of the psychogram since it was not utilized in the scoring of these records. The fact that it was not necessary to use this symbol is in itself significant, for it means that this aspect of personality was entirely absent from the makeup of these patients. Since this type of response epitomizes the ability to introspect, to "know oneself," an interesting

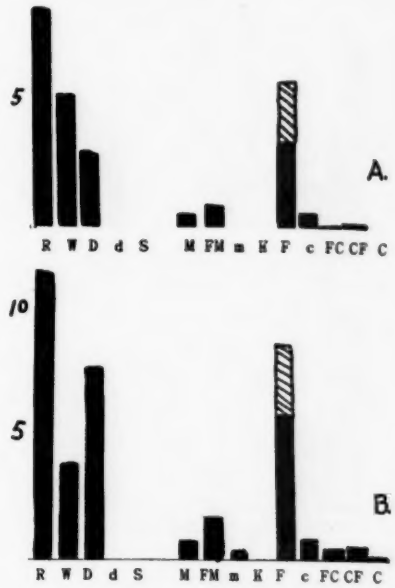

Fig. 8.—*A*, composite record of 10 patients with tumor of the brain on preoperative Rorschach examination. *B*, composite graph from 10 postoperative records.

parallel may be found between these results and those obtained by Freeman and Watts,[17] who claimed:

> Many of the symptoms of frontal lobe disease can be explained on the basis that the individual has lost his self-critique, is more easily satisfied, is lacking in "social sense," has had an impairment of his imagination as related to himself.

Figure 8 (records of all patients examined preoperatively as compared with those of all patients examined postoperatively, regardless of the type or location of the tumor) shows that the postoperative

17. Freeman, W., and Watts, J. W.: An Interpretation of the Functions of the Frontal Lobe Based upon Observations in Forty-Eight Cases of Prefrontal Lobectomy, Yale J. Biol. & Med. **11**:527-539, 1939.

records are slightly better than the preoperative. Since all but 3 of the 18 postoperative records were the result of the patient's first contact with the cards, this improvement cannot be ascribed to the effect of practice.[18]

This slight improvement may be noticed in (1) an increase in the number of *D* responses, that is, some measure of analytic thinking offsetting the vague generalization of the predominantly *W* approach; (2) an increase in the proportion of *F* plus responses; (3) the emergence of some responses of the *FC*, *CF* type, that is, a slight expansion of the personality on the affective side, and (4) a slight increase in the *M* and *FM* responses, again representing a slight dilation of the personality.

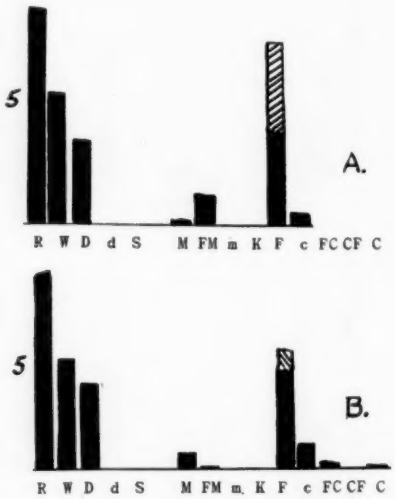

Fig. 9.—*A*, composite record of 4 patients with tumor of the frontal lobe on preoperative Rorschach examination. *B*, composite graph from 5 postoperative records of patients with tumor similarly located.

Figure 9 (record for patients with lesions of the frontal lobes) may be compared with figure 10 (record for patients with lesions of the parietal lobes). The constriction of personality is more marked with lesions of the frontal lobe. Figure 10 *B*, the postoperative record of a patient with a parietal lesion, approximates a certain type of normal record more closely than it does the composite picture in figure 7. It may advantageously be compared with figure 5 *A*, which is the record of a maid in the hospital of the same age and of a somewhat similar

18. This effect may be partially due to the influence of the one postoperative record of a patient with a parietal lesion, which is the most "atypical" and might well have been given by a normal person of low intelligence.

economic and educational background. It is also interesting to notice that the lesion in this case was a meningeal fibroblastoma which had been completely removed at operation.

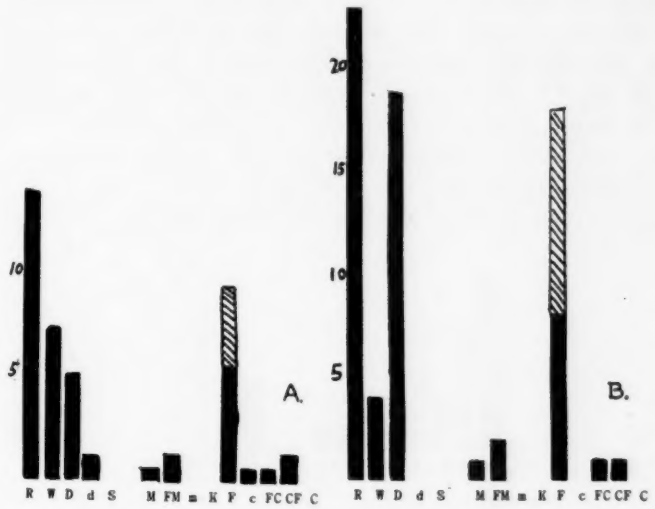

Fig. 10.—Records of patients with tumor of the parietal lobe. *A*, composite record of 3 patients examined preoperatively; *B*, record of 1 patient examined postoperatively.

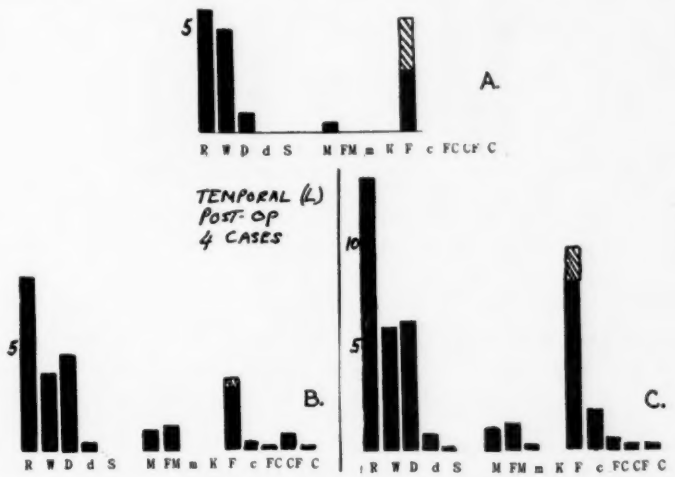

Fig. 11.—Records in cases of tumor of the temporal lobes. *A*, composite preoperative record of 2 patients with lesions of the right temporal lobe. *B*, composite graph from 4 postoperative records of patients with lesions of the left temporal lobe; *C*, composite graph from 4 postoperative records of patients with lesions of the right temporal lobe.

In the records of patients with lesions of the temporal lobe (fig. 11) one finds again the consistent, though slight, superiority of the post-

operative records which appears throughout. The postoperative records of the patients with lesions of the temporal lobe were analyzed in terms of right and left, since 3 of the 4 patients with the left temporal lobe removed were somewhat aphastic at the time of investigation. That this condition does not essentially alter the responses will be shown in a separate discussion; nevertheless, there is sufficient difference between the postoperative records of patients with lesions of the right and those with lesions of the left temporal lobe to warrant the difference in the composite pictures. All other locations yielded such minute differences, when examined according to the side of occurrence of the lesion, that they have not been illustrated. The postoperative composite picture for patients

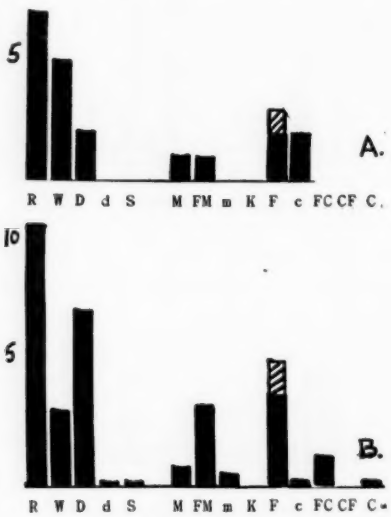

Fig. 12.—Records of patients with tumor of the occipital lobe. *A*, preoperative record of 1 patient; *B*, composite graph from 4 postoperative records.

with lesions of the right temporal lobe can be seen to indicate a slightly greater output and has a definite scoring in terms of *c*. This would indicate a greater sensitivity, a greater anxiety or concern on the part of the patient for his own condition and a greater awareness of the gravity of the situation than are found elsewhere. This was clearly seen in the comparison of 2 individual cases. A clinical comment on 1 patient with a lesion of the left temporal lobe was that he showed no interest or concern in knowing the result of the operation and had made no inquiries as to his condition. Anxiety for a return to normal was well illustrated in the case of 1 patient with a lesion of the right temporal lobe, who was apprehensive lest the test reveal some mental abnormality.

The composite postoperative records of patients with occipital lesions and the single preoperative record of a patient with an occipital lesion did not show any particular distinguishing characteristics. The postoperative picture is possibly less abnormal than that with the other types of tumor, but the difference is slight. In summarizing the differences between the four locations, it can be said that if any area stands out from the others as associated with the greatest deviation from the composite picture shown in figure 7, it is the parietal region. This is apparent particularly in the postoperative record of the case in which there was complete removal of a meningeal fibroblastoma. Perhaps the records of

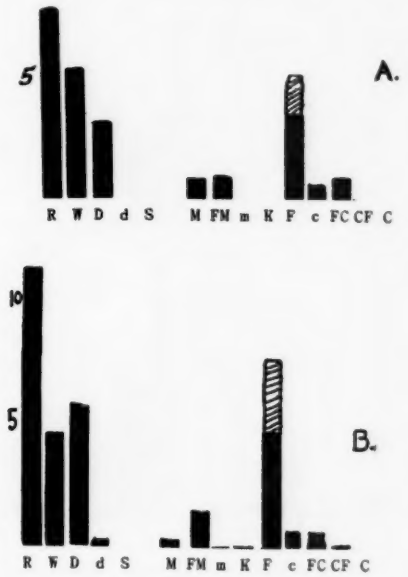

Fig. 13.—*A*, composite graph from 10 records of patients with rapidly growing tumors. Some of the patients were examined preoperatively and some postoperatively. *B*, composite graph from 18 records of patients with slowly growing tumors. Some of the patients were examined preoperatively and some postoperatively.

patients with occipital lesions can be said to show less constriction than those of patients with frontal lesions, but in general there is little choice between the locations. All the records deviate markedly from the normal record shown in figure 2 and the composite picture in figure 3 *B*. This does not mean, however, that a more detailed and qualitative analysis of patients with lesions of the frontal lobe, for example, may not in certain cases indicate differences between them and patients with lesions of other areas. A differentiating study is in progress.

When the group was divided in terms of the pathologic character of the lesion, that is, into patients with rapidly growing and patients with slowly growing tumors, there was again little choice between the four composite records. While the output was slightly greater with the slowly growing tumors (fig. 13 *B*), there was a slightly larger percentage of poor form responses. When each group is again subdivided in terms of the preoperative and the postoperative status of the patient, the postoperative picture is slightly better than the preoperative one, but there are certainly no significant differences referable to the type of tumors.

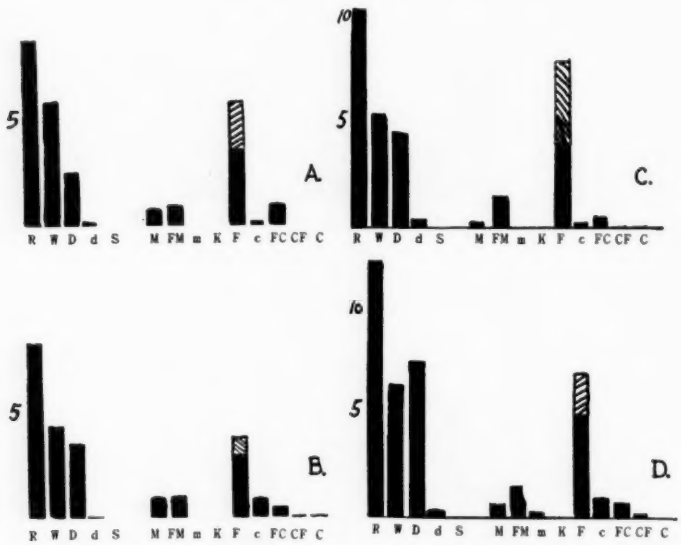

Fig. 14.—*A*, composite record of 3 patients with rapidly growing lesions, examined preoperatively. *B*, composite graph from 7 postoperative records of patients with rapidly growing lesions. *C*, composite record of 7 patients with slowly growing lesions, examined preoperatively. *D*, composite graph from 11 postoperative records of patients with slowly growing lesions.

Figure 15 illustrates 8 individual records of patients with tumor. A comparison of these with any of the individual records given in figures 4 and 5 will bring out clearly the uniformity and similarity of these records as compared with the diversity and comparative richness of all the normal records.

Figures 16 and 17 illustrate interesting individual cases. Figure 16 is a record taken fully one year postoperatively. In this case the right frontal lobe had been removed for a glioblastoma multiforme. The record obviously is one which bears out the characteristics one has come to

expect in such a case. The interesting point in this case, however, is that the patient received a score on the Binet scale of "superior adult II." She did well in a series of performance tests, and when the Kohs blocks were used (according to Goldstein's procedure) she still showed no detectable loss of abstract attitude. This patient was back at work, tending a village store by herself. That there was no strictly

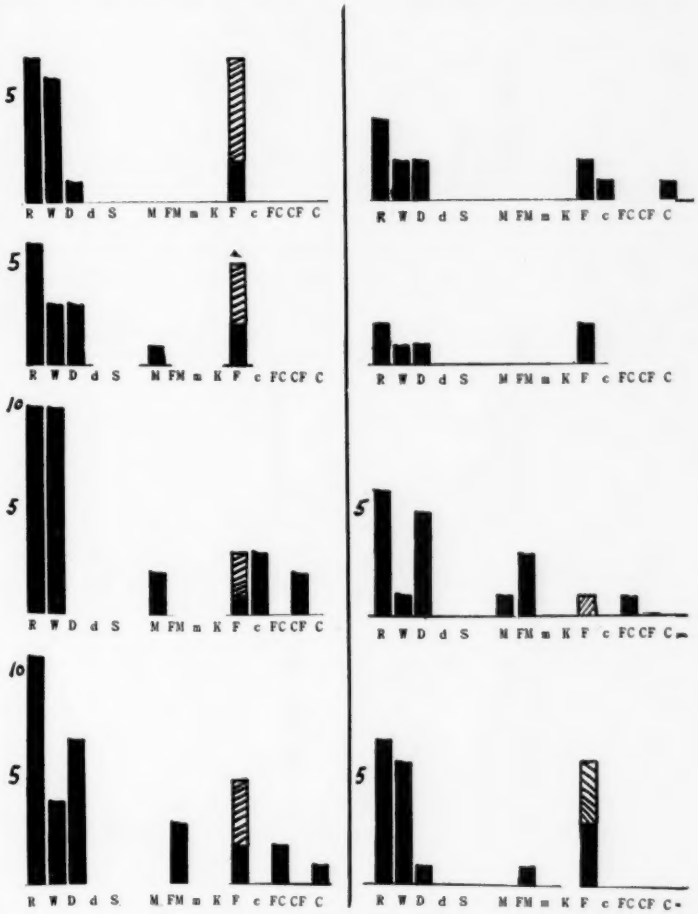

Fig. 15.—Eight individual records of patients with tumor. Note the uniformity and similarity of these as compared with all the normal records.

intellectual deterioration is seen by the fact that her *F* responses were all plus (good and accurately perceived forms), but the restricted output and the constricted range of responses, despite the capacity, show the typical picture of tumor.]

The preoperative and postoperative records of the patient whose case is illustrated in figure 17 are included here because of the interesting fact that despite an enormous superficial change in the patient's manner after the operation, the two records are remarkably similar. A few days before the operation this patient took the test, but, although cooperative and comparatively alert, he was depressed by a severe headache. Eight days after the operation he was up and about, delighted at

Fig. 16.—Record of a patient in whom the right frontal lobe had been removed for a glioblastoma multiforme. This record was made fully a year after the operation.

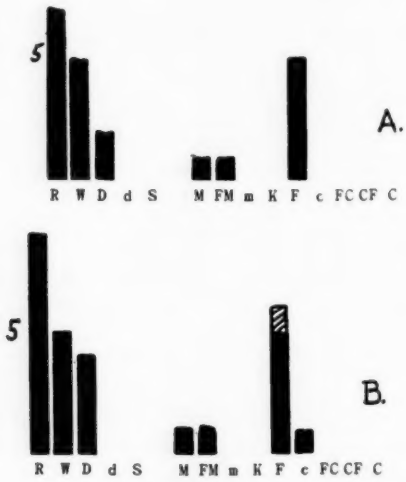

Fig. 17.—Preoperative (*A*) and postoperative (*B*) records of the same patient, A. C.

his rapid improvement and freedom from headache, bright and cheerful. His improved physical condition at that stage makes little difference and does not alter the basic personality pattern.

Figure 18 is included to show a marked change when records were taken preoperatively, immediately postoperatively and after one year. The patient had a cystic astrocytoma of the left frontal lobe, which was removed at operation. There was a distinct and immediate postoperative improvement over the preoperative record, and marked improvement was observed at the end of the first year. This improvement,

however, was in one sphere only, the more strictly intellectual. Despite the increase in *F* plus responses, the greater output and the better mental approach one would be suspicious of the final record in that there was still virtually no response on the affective side. There is an interesting parallel between these records and other information concerning this patient. His intelligence quotient, even shortly after oper-

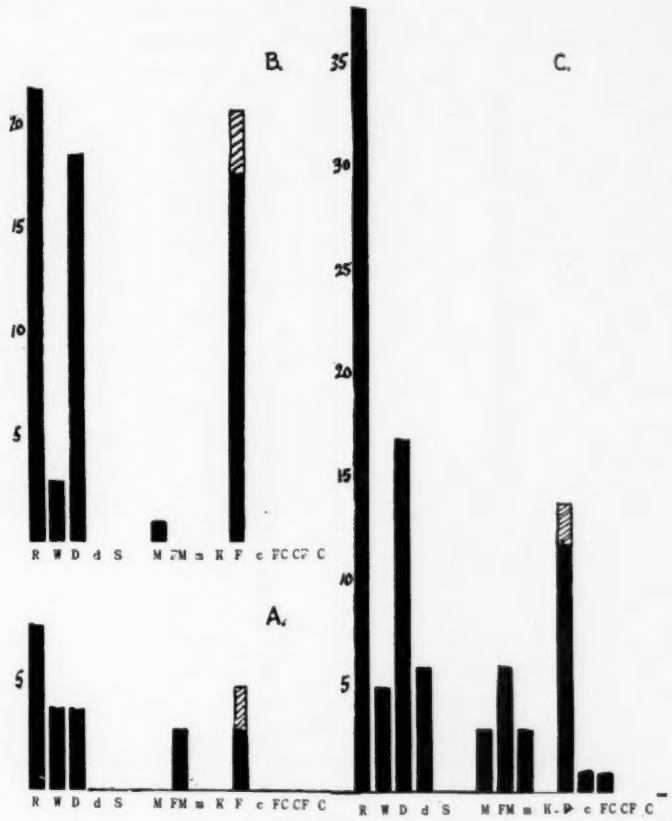

Fig. 18.—Records made (*A*) preoperatively, (*B*) immediately after the operation and (*C*) one year after the operation in the case of M. L., a patient from whom a cystic astrocytoma of the left frontal lobe had been removed.

ation, was 124, and one year later it was 131. However, at the time the third Rorschach record was taken, though capable of being back at work, he presented a behavior problem, with marked antisocial tendencies. Hebb,[19] who has considered this patient in a recent article, raised the question "whether the ability of these three men [of whom

19. Hebb, D. O.: Intelligence in Man After Large Removals of Cerebral Tissue: Report of Four Left Frontal Lobe Cases, J. Gen. Psychol. **21**:73-87, 1939.

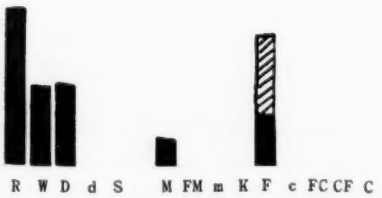

Fig. 19.—Record of M. B. This is a particularly clear record. The interesting thing about this case was that the clinical diagnosis had been involutional melancholia. The first neurologic signs (changes in the eyegrounds) were noted independently on the day the Rorschach test was given. Operation subsequently revealed a bilateral frontal meningeal fibroblastoma. This is a case in which a correct diagnosis was made from the Rorschach test, in the face of the clinical picture as reported at the time of psychologic examination.

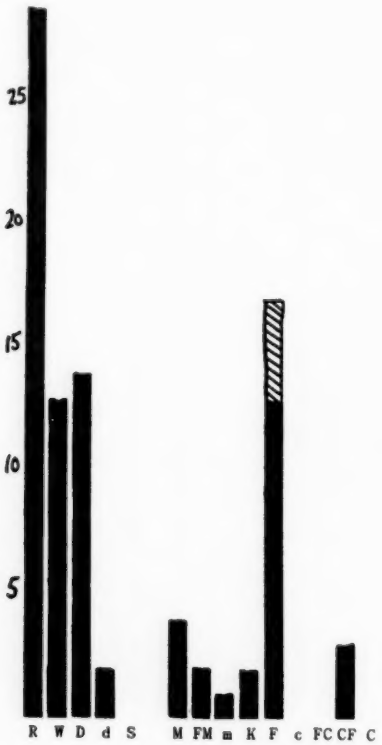

Fig. 20.—Record of H. S. The provisional clinical diagnosis was tumor of the frontal lobe. From the Rorschach record this will be seen to be unlikely. On comparison with figure 7 it will be seen that the output is much greater and the *M* column too high; both *m* and *K* are represented in this record and do not appear at all in the composite record of patients with tumor, while the percentage of *F* responses is in the normal range. This record, then, does not show the constriction or the high *F* percentage shown by the composite record of patients with tumor, particularly of patients with tumor of the frontal lobe examined preoperatively. Furthermore, the anxiety evidenced in the *K* responses may well be concerning the patient's own condition, a type of response "conspicuous by its absence" in the records of patients with tumor of the frontal lobe.

The final diagnosis was retrobulbar neuritis and multiple sclerosis.

this patient is one] to adjust themselves economically and socially is on the same plane as their intelligence test scores." The Rorschach record and the subsequent history would indicate that this question would have to be answered in the negative as far as this patient is concerned.

THE RORSCHACH METHOD IN DIFFERENTIAL DIAGNOSIS

Turning now to the second general question raised at the beginning of the paper, one may ask how reliable these composite pictures are in the differential diagnosis of tumor of the brain.

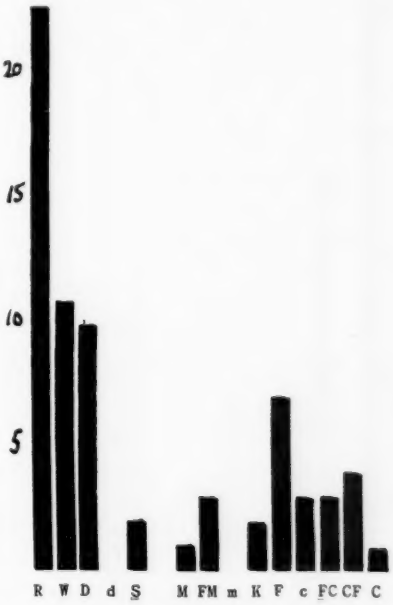

Fig. 21.—Record of R. S. Comparison of this record with figure 7 immediately shows that the *FC*, *CF* and *C* responses are far too high to permit its inclusion with the records of patients with cerebral tumor. Moreover, the proportion of good form responses is 100 per cent, and the anxiety indicated by the *K* responses is not found in figure 7. The final conclusion in this case was that the headache and other physical symptoms were part of a neurosis.

The clinical problem with which the psychologist is confronted is frequently one in which a tumor of the brain is suspected, clinical evidence having been sufficient to warrant a neurologic examination but no final diagnosis having been reached. The Rorschach psychodiagnostic test, it seems to me, can be advantageously used to distinguish between an alteration of personality due to a cerebral lesion and one that

bears the hallmarks of the neurotic person, and to differentiate both of these from the condition of a person who is psychologically normal. Further clinical examination may confirm the presence of a tumor or other cerebral lesion, discover the symptoms to be of neurotic origin or ascribe the headache to malformation of the skull or to an extracerebral lesion. Both for the practical advantage of an additional diagnostic method and for ultimate understanding of the relation between actual cortical conditions and the accompanying psychologic phenomena,

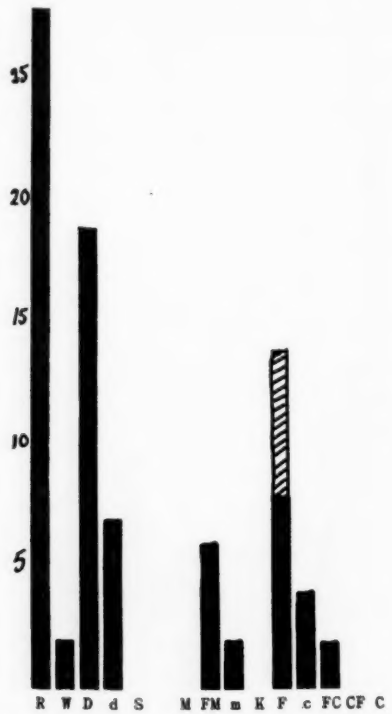

Fig. 22.—Record of D. W. This patient was being examined for possible tumor as the cause of headaches.

On comparison with figure 7 it will be seen that this record does not belong in the "tumor group." The output is too great and the $W:D:d$ ratio quite different. The *FM*, *m* and *c* columns all bespeak a personality very different from that epitomized in figure 7. Examination revealed that the patient was syphilitic and pregnant.

repeated and careful parallel studies of clinical conditions and the accompanying Rorschach picture would seem to be of value.

The comparison of the Rorschach record of a "tumor suspect" patient with the established composite picture of patients with tumor (fig. 7) affords one criterion for determining the presence of a cerebral

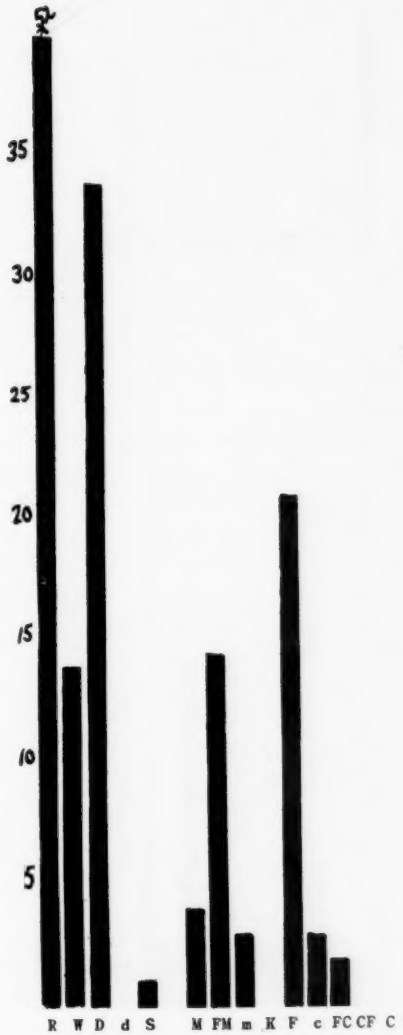

Fig. 23.—Another clear example of a record which does not belong in the "tumor group," despite the fact that the patient was under observation for a possible cerebral lesion as a cause of headache. It can be seen at a glance that this record contains none of the characteristics of the record of a patient with a cerebral tumor. Although the ultimate diagnosis in this case was deferred, it was felt that the question of cerebral lesion had been ruled out by the neurologic examination. This record, incidentally, would lead one to suspect a behavior problem in this girl of 16, whose more primitive drives (as exemplified in the *FM* score) so markedly outweighed the *M* score and the sum of whose emotional responses was so low.

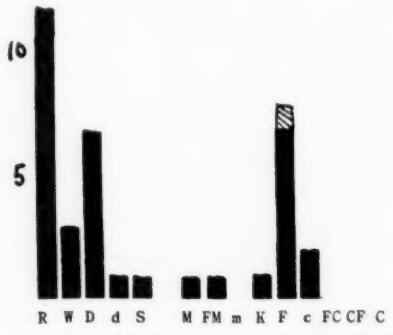

Fig. 24.—Record of S. T. This patient was being examined for the cause of severe headache. At first sight it would seem as if this record might belong in the "tumor group," but closer examination reveals that, despite the restricted output and the lack of all *FC*, *CF* and *C* responses, there are factors which make a cerebral lesion unlikely.

The *W*:*D*:*d* ratio is essentially normal. The percentage of *F* — *F* responses is low, in the normal range. *K* and *c* are represented. The final diagnosis was that of developmental cranial anomaly (craniostenosis).

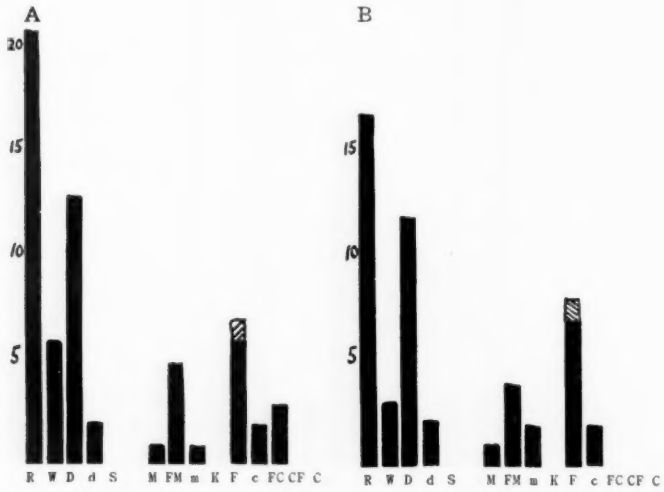

Fig. 25.—Record in a case which is included because it was an example of incorrect diagnosis. The first record (*A*), taken preoperatively, did not present the typical tumor picture according to our criteria and showed none of Piotrowski's ten signs. At operation, however, a tumor less than 2 cm. in diameter was found. This was completely removed. Although this constitutes a failure of the technic in one sense, it is particularly important in that it serves to show that a small lesion need not immediately produce changes in personality. This patient, both before and after operation, was considered completely normal in every way by immediate relatives. The postoperative record (*B*) is included in the various composite pictures of patients with tumor. It shows no effect of practice, there being actual reduction in output over that shown by the first record.

lesion. I also employed Piotrowski's ten signs as a further check. In general, the results from my method and from that suggested by Piotrowski were in agreement, but there were cases in my "preoperative tumor group" in which there were only two or three signs, yet in which the patients undoubtedly belonged among those with tumor when graphic studies were made.[20]

The records in figures 19 to 25 should be compared with those for the normal group, in figure 3 *B*, and with the composite picture for the "tumor group," in figure 7.

COMMENT

If one is satisfied that these various records of patients with tumor, both as composite and as individual pictures, differ from the various records of normal persons, one must still discuss the differences in terms of the type of person who gives the particular record.

The outstanding characteristics of the records of patients with tumor are their uniformity and constriction. The uniformity would make one think that all the patients had been submitted to similar conditions, so that this common influence resulted in a uniform personality structure despite differences in age, sex, education and experience. The constriction would make one think that perhaps, in order to carry on the mere business of living under difficult conditions, the organism discarded all but the most necessary types of responses and clung tenaciously to them. This would result in flattening out of psychic potentialities, diminishing of the individual aspects of the person and resorting to the most obvious, and therefore the safest, type of response. It is as if the patient had lost interest in all the finer details of the business of living and held only to a few necessary guideposts of normality.

The question of how this change in personality comes about and what are the necessary conditions for it is important. It seems to me that there are three possibilities: 1. The personality of the patient may be changed as a direct result of the removal of brain tissue. 2. The personality may be changed owing to the direct effects of pathologic alteration of cerebral structure and function. 3. The external environment during illness and hospitalization may affect personality; i. e., one might require for thorough understanding of the change in personality a consideration of psychologic as well as neurologic factors. Cobb[21]

20. One type of record, for example, may show Piotrowski's [7] *R* and *M* responses but no other signs. That is, the responses given, though few and containing only 1 *M*, are of good form. Sometimes the P (or "popular") percentage of such records is 100, instead of less than 25 found by Piotrowski. In these records there will be no *Ap, Cn, Rpt, Imp, Plx* or *T*.

21. Cobb, S., and Cohen, M. E.: The Use of Hypnosis in the Study of the Acid-Base Balance of the Blood in a Patient with Hysterical Hyperventilation, A. Research Nerv. & Ment. Dis., Proc. (1938) **19**:318, 1939.

and others interested in psychosomatic relations have repeatedly emphasized this in other connections.

In the third instance the disease might, over a period of time, cause general physical or neurologic symptoms and, directly or indirectly, psychologic symptoms, so as to introduce restrictions and limitations into the patient's life. So far as the patient was physically improved after the removal or partial removal of the tumor (by the reduction of intracranial pressure, the relief of headache and other such factors) one might expect the postoperative psychologic performance to be somewhat better than the preoperative, but return to normal would invariably require time and would depend on many psychologic as well as neurologic and other physical factors. Thus, even excellent recovery with absence of neurologic signs and lack of evidence of the recurrence of pathologic cerebral change would not necessarily result in a normal Rorschach picture even years after the operation. The psychologic components of the original illness might have left an indelible impression, and it would always be difficult to tell whether these psychologic changes were caused by the cerebral lesion or by the memories, fears and other situational factors active at the time of hospitalization and operation.

How do the results fit in with these suggested alternatives? If the first is true, namely, that the mere absence of tissue was responsible for the change, then all preoperative records should be better than postoperative ones, for the removal constitutes the abnormality and the absence of a certain area of cortical tissue is directly connected with the changed personality picture.

If the second alternative is true, namely, that the only and necessary cause for a change in personality is the presence of abnormal tissue, then postoperative records after complete removal of such tissue should show a normal picture as soon as the cerebral edema of the postoperative period has subsided, while records of patients in whom gross pathologic tissue remains should continue to show the abnormal picture.

If the third alternative is nearest the truth, namely, that neurologic and psychologic factors are inseparably interrelated and mutually influential, then after a time, provided no pathologic tissue is present and the psychologic experience of the operation has been successfully incorporated in the patient's life scheme, improvement over both the preoperative and the immediate postoperative record may be expected. However, this improvement would not necessarily follow a satisfactory operative procedure if the psychologic components of the equation weigh too heavily against it. It is not possible at this stage, without a consideration of the records of patients with focal epilepsy in whom clean removals of scar tissue have been made, to do more than point out that my results are definitely against the first explanation. There is no

question of sudden abnormalities appearing in the records after the removal of the tissue. Rather, the postoperative records are, if anything, slightly better than the preoperative ones. In these cases of cerebral tumor, then, the psychologic changes, to whatever they were due, must be considered as having existed preoperatively and having continued immediately after the operation, though in most cases in which the testing was done postoperatively they were less pronounced. Removal of an area of cerebral tissue was certainly not alone responsible for the abnormal Rorschach picture. This would bear out the observations of Jefferson,[22] who claimed that patients who showed no psychologic changes before operation presented none after the removal of one frontal lobe. My comment here, however, would be that, in all probability, had Rorschach records been obtained from Jefferson's patients before operation evidence of some restriction of psychic reactivity would have come to light, even though, as with my patients, it is frequently not evident in their everyday behavior, or even with standard intelligence and performance tests.

SUMMARY AND CONCLUSIONS

Examination of the Rorschach records of patients with cerebral tumors has shown that both as composite pictures and as individual records they differ markedly from the normal. Twenty-eight records of 25 patients with tumors of the brain, even when expressed in graphic form only, show restricted and constricted personality, extraordinarily uniform when contrasted with the variety found in the records of the normal subjects.

When considered in terms of the preoperative and postoperative status of the patient, the records of the postoperative group were found to be slightly superior.

When considered in terms of the pathologic character of the lesion, the slowly growing and rapidly growing tumors, the records showed no significant difference.

The location of the lesion was not an important factor. Twenty-six of the 28 records differed so greatly and consistently from the normal records that the smaller differences between records of patients with lesions in various locations were relatively insignificant. However, further differential studies are necessary and are in progress.

In differential diagnosis, one finds that the Rorschach method may be useful in distinguishing between a cerebral lesion and conditions with symptoms simulating this condition.

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22. Jefferson, G.: Removal of Right or Left Frontal Lobes in Man, Brit. M. J. **2**:199-206, 1937.

The attempt to differentiate more exactly within the group of patients spoken of in the Rorschach literature as having "organic" lesions can be completed only when this comparatively uniform group of patients with cerebral tumors is compared with groups of persons with cerebral lesions of other types. In a subsequent paper the preoperative and postoperative studies of patients with tumors will be compared with similar studies of patients with focal epilepsy. Moreover, the general discussion concerning the relation of the personality picture as presented in the Rorschach test and the actual underlying cortical condition will be reserved until all the evidence has been presented.

VASCULAR BED OF THE RETINA IN MENTAL DISEASE

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AND
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The circulatory apparatus is one of the most important integrating systems of the body, since by means of its channels it distributes oxygen, nourishment, enzymes, hormones and other chemical substances to the tissues, makes internal respiration possible, takes a major part in immunity and resistance to disease and neutralizes or removes the end products of metabolism; in fact, its known vital functions are too numerous to mention here.

For many years that other great integrating system, the brain with its neural extensions, has been studied intensively in relation to mental disorders, but the structure and function of the circulatory system have attracted comparatively little similar attention in this connection. It is probable that numerous investigations in the physiology, as such, of the circulatory system have a bearing on mental disorders that will eventually be brought into the picture in elucidating the field of psychiatry. Of those investigations within the field, a few have shown clinical evidence of vasomotor disturbances and structural inadequacies as characteristics of the circulatory apparatus.

In 1923 and in 1925 one of us (N. D. C. L.) [1] reported on the basis of postmortem examinations that the average weight of the heart of persons with catatonic-hebephrenic dementia praecox is about one-third less than that of the normal or average person, the small size being independent of race, age, sex, size of body, duration of psychosis or

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From the New York State Psychiatric Institute and Hospital (Dr. Cotton and Dr. Lewis), and the Institute of Ophthalmology of the Presbyterian Hospital of the City of New York (Dr. Egenhofer).

This work was supported by a grant from the Committee on Research in Dementia Praecox founded by the Supreme Council, 33d Degree Scottish Rite, Northern Masonic Jurisdiction, U. S. A.

1. Lewis, N. D. C.: Constitutional Factors in Dementia Praecox with Particular Attention to the Circulatory System and to Some of the Endocrine Glands, Nervous and Mental Disease Monograph 35, Washington, D. C., Nervous and Mental Disease Publishing Company, 1923; An Anatomical Study Contrasting the Dementia Praecox Constitution with That of Paranoid Developments, South. M. J. **16**:327, 1923; Comments on the Pathology of Dementia Praecox, J. Nerv. & Ment. Dis. **62**:225, 1925.

lethal lesion. This decrease in size was interpreted as hypoplasia or arrest in growth. In addition to the hypoplasia, atrophy is also present and to be expected in subjects dying of tuberculosis and other regressive diseases. The heart valves develop normally and are free from lesions. Although occasionally secondary atrophy in the muscle is present, the original arrest in growth was indicated by the small aorta with its correspondingly small branches. This type of circulatory system tended to retain its small proportions throughout life and seemed to lack the capacity to develop a true compensatory hypertrophy. The walls of the congenitally hypoplastic aorta are usually thin, smooth, free from lesions and hyperelastic. Associated with this anatomic state is a wide bed of lymphatic channels, often to the extent suggestive of the larval state of the status lymphaticus syndrome.

In contrast to this picture, which is characteristic of the regressive psychoses, is the anatomically large circulatory system, with its tendency to varicosities, formation of aneurysms, cerebral and other hemorrhages, cardiac hypertrophy and decompensation, in the paranoid and manic-depressive types. These types were referred to as hypercompensatory psychoses. The state of the circulatory apparatus in these two groups of disorders was not considered as playing the role of a definite cause in mental disease, but was regarded as a part of a constitutional organization which predisposes and might in part determine the reaction type.[2]

Studies on the blood volume in cases of schizophrenia have been made by Looney and Freeman [3] and by Finkelman and Haffron.[4] These authors have found indications of circulatory disturbance. The Elgin workers found a low circulating blood volume in patients with dementia praecox as compared with the normal values for their patients with manic-depressive psychoses. In their opinion this diminution in the blood volume is related to disorders in water metabolism, capillary permeability, vasomotor tonus, secretion of the antidiuretic and vasopressor hormones of the posterior lobe of the pituitary gland, basal oxygen consumption rate and heat regulation, which processes are influenced by the hypothalamic centers. The basal blood pressure and other pertinent phenomena have been investigated to some extent, and several features have been studied and discussed by Hoskins [5] and his co-workers in a number of publications during the past ten years.

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2. Lewis, N. D. C.: The Pathology of Mental Disorders, New York State J. Med. **36**:1, 1936.

3. Looney, J. M., and Freeman, H.: Volume of Blood in Normal Subjects and in Patients with Schizophrenia, Arch. Neurol. & Psychiat. **34**:956 (Nov.) 1935.

4. Finkelman, I., and Haffron, D.: Estimation of the Circulating Blood Volume in Schizophrenia, Collect. & Contrib. Papers, Elgin State Hosp. **2**:73, 1936.

5. Hoskins, R. G.: Problem of Mental Disorder, New York, McGraw-Hill Book Company, 1934, chap. 11.

In the course of an extensive investigation of the vascular system in mental disease from both the morphologic and the physiologic point of view, we thought it of primary importance to study the developmental and anatomic status of the vascular system. In addition, we hoped to be able to establish a reliable index of these factors in the individual patient. Studies of this nature in the living human body present many experimental and technical difficulties.

Many avenues of approach have been tested and found unsatisfactory, either because the area studied failed to represent the general vascular situation or because the technical limitations of the method utilized made generalization impossible. There have been a number of studies on the capillary loops of the base of the nail, and at one time it was stated that a definite relationship did exist between the structure of the capillary loop and the type of functioning vascular system.[6] However, recent studies [7] on a large group of patients have shown that the capillary loops vary greatly in both length and diameter with such uncontrollable factors as occupation, frequency of hand washing and general habits. These difficulties invalidate such mensuration studies as indexes of the anatomic status of the general vascular tree.

Roentgen visualization of representative vessels of the vascular tree by means of the introduction of radio-opaque substances directly into the venous or the arterial system has not yet reached the state at which reliable results can be obtained without danger to the subject.

After surveying the possible methods of approach, we recalled that the blood vessels of the retina offer the most direct field for investigation. For years the diagnostician has considered examination of the eyegrounds an essential part of the examination of the vascular system. Here, under direct vision with the ophthalmoscope, one may observe sharply the total vascularity of an individual organ. Since measurement of the vascular bed is our primary concern, the problem is simplified by the fact that the branches of the central artery of the retina furnish the sole blood supply of this organ, with the exception of one minute cilioretinary branch to the macula lutea. The vessels are all end arteries, and the question of collateral circulation does not complicate the problem. In addition, it is believed that study of the retinal arteries is particularly valuable in the investigation of conditions associated with the disturbance of mental function. The central artery of the retina is the direct continuation of the last branch of the internal carotid artery before it divides into the anterior cerebral vessels, and it is structurally similar to the vessels of the brain.

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6. Müller, O.: Die Capillaren der menschlichen Korperoberfläche, Stuttgart, Ferdinand Enke, 1922.

7. Jamin, F.: Capillaries of the Nail Bed in Relationship to Constitutional Peculiarities, Ztschr. f. d. ges. Neurol. u. Psychiat. **131**:114, 1936.

METHOD AND MATERIAL

With this idea in mind, we made a study of the various methods in use for measuring structures on the background of the eye. After considerable experimentation we devised a modification of the method recently described by Lobeck.[8]

In both Lobeck's original method and our modification measurements are made with a special measuring eyepiece on the Gullstrand ophthalmoscope. This eyepiece is constructed on the principle of the heliometer and is graduated to intervals of 0.01 mm. The image of the fundus is modified by the refraction of the light passing through the various media of the eye. The amount of this modification varies in different persons with differences in refractive error. Lobeck corrected for this variability by measuring the horizontal diameter of the image of the optic disk. He assumed that this diameter is actually 1.5 mm. and by the relationship of the observed value to this assumed constant determined the factor of magnification. This correction for magnification is applied to the measurements of the images of the retinal vessels. We soon discovered that this method allowed too large an error, because the true disk diameter varied from 1.2 to 1.7 mm. (average 1.43 mm.) in a small group of cases.

In our modification of the Lobeck method the full refracting power of each eye is first determined, and, by means of a formula that takes into account the refraction of the eye and of the lenses of the ophthalmoscope, the exact magnification factor is determined. When this factor is applied to our readings from the micrometer eyepiece, we have accurate measurements on the fundus of the eye, free from any assumed values. A full account of this method is being published in a separate paper.

Lobeck, Neame, Kuhn and Badtke[9] have studied primarily the diameter of individual arteries and have listed characteristic values for the retinal vessels at the margin of the optic disk in the normal and in certain pathologic states. Because of the inconstant and individual method of branching of the retinal arteries, one eye may contain ten such vessels and another five. We therefore think that measurements of individual arteries cannot be of any value when comparative studies are made or when there is a desire to study the status of the general vascular system. Therefore, we have measured the diameter of each vessel at the margin of the optic disk and have computed the cross sectional area of each vessel at this point. The sum of these values, then, represents the cross sectional area of the vascular bed of the retina at a constant point and, it is believed, will reflect the general developmental and morphologic status of the vascular component of the individual constitution.

In this preliminary study a series of 26 patients at the New York State Psychiatric Institute and Hospital were examined. Eighteen were suffering from some form of mental disease diagnosed as dementia praecox, while 8 were designated as manic-depressive patients. Refraction of both eyes of all subjects was

8. Lobeck, E.: Diameter of the Retinal Vessels in Health and Disease, Arch. f. Ophth. **136**:439, 1937; Diameter of the Retinal Vessels: A Clinical Study, Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **51**:400, 1936.

9. Neame, H.: A Method of Estimating the Caliber of the Arteries of the Eye, Tr. Ophth. Soc. U. Kingdom **56**:155, 1936. Kuhn, W.: Measurements of the Background of the Eye, Arch. f. Ophth. **138**:129, 1937. Badtke, G.: Measurements of the Caliber of the Retinal Vessels in Hypertension and Renal Disease, Klin. Monatsbl. f. Augenh. **99**:655, 1937.

done under homatropine cycloplegia, and the measurements of the vessels were made immediately afterward. During the same examination the blood pressure was measured in both the sitting and the lying position in order to rule out cases of hypertension. Blood chemistry studies and urinalysis were made in all cases to rule out those organic conditions which may alter the vascular structure of the

TABLE 1.—*Patients with Mental Disease Arranged According to Caliber of Retinal Vascular System*

Sex	Age, Yr.	Retinal Vascular Bed, Sq. Mm.	Diagnosis	Duration, Mo.	Habitus	Clinical Status*
F	24	0.0104	Catatonic-hebephrenic schizophrenia	45	Pyknic	Deteriorated
M	19	0.0148	Hebephrenic schizophrenia	36	Undifferentiated	Deteriorated
M	21	0.0152	Simple schizophrenia	24	Undifferentiated	Deteriorated
F	17	0.0163	Hebephrenic schizophrenia	42	Pyknic	Deteriorated
M	31	0.0166	Hebephrenic schizophrenia	24	Pyknic	Circumscribed improvement
F	27	0.0174	Catatonic schizophrenia	6	Asthenic	Marked improvement
M	16	0.0181	Hebephrenic schizophrenia	30	Asthenic	Circumscribed improvement
M	22	0.0185	Hebephrenic schizophrenia	48	Asthenic	Improving
F	21	0.0185	Manic-depressive psychosis, depressed	8	Asthenic	Recovered
M	18	0.0190	Manic-depressive psychosis, depressed	3	Undifferentiated	Recovered
M	33	0.0193	Paranoid schizophrenia	54	Dysplastic	Circumscribed improvement
M	24	0.0194	Paranoid schizophrenia	4	Pyknic	Deteriorated
F	23	0.0207	Catatonic schizophrenia	8	Pyknic	Circumscribed improvement
F	20	0.0208	Catatonic schizophrenia	8	Asthenic	Improving
M	27	0.0210	Manic-depressive psychosis, manic	3	Undifferentiated	Recovered
F	36	0.0212	Manic-depressive psychosis, depressed	3	Undifferentiated	Recovered
M	48	0.0221	Manic-depressive psychosis, manic	3	Asthenic	Recovered
F	32	0.0223	Manic-depressive psychosis, depressed	10	Undifferentiated	Improving
M	19	0.0226	Simple schizophrenia	10	Undifferentiated	Improving
M	18	0.0230	Hebephrenic schizophrenia	60	Asthenic	Deteriorated
F	21	0.0231	Catatonic schizophrenia	4	Undifferentiated	Marked improvement
M	20	0.0235	Manic-depressive psychosis, manic	5	Dysplastic	Recovered
M	31	0.0254	Catatonic schizophrenia	8	Asthenic	Marked improvement
M	29	0.0258	Paranoid schizophrenia	8	Undiffenentiated	Unimproved
F	20	0.0285	Hebephrenic schizophrenia	11	Asthenic	Improving
F	18	0.0361	Manic-depressive psychosis, depressed	4	Pyknic	Recovered

* In this table and in the accompanying tables, the term "circumscribed improvement" has been used to designate those patients who have made an adjustment within the hospital on a higher level than in the situation present before admission. Delusional symptoms continue unimproved, and the clinical staff feels that the prognosis for full recovery is poor in these cases.

The term "improving" is used to designate those patients who have been under observation only a short time but whose clinical condition has been marked by progressive steady improvement. The clinical staff feels that the prognosis for full recovery is good in these cases.

eye. The eye was examined for any local pathologic lesion, and all cases were excluded in which there was any possible local alteration of vascularity. The height was measured with the patient in the standard anthropometric position, and the weight was determined by taking the most constant weight, in kilograms, over an extended period. Observations and judgments as to the diagnosis and clinical status in each case were made by the clinical staff independent of this investigation.

RESULTS

In table 1 the patients have been arranged in order of increasing caliber of the total retinal vascular system. One quickly sees that the manic-depressive patients are not to be separated from the schizophrenic patients. The mean value for the measurements of the vascular bed for the manic-depressive group is 0.0230 sq. mm. (standard deviation, 0.0094), and this is slightly higher than the value for the schizophrenic patients, which is 0.0198 sq. mm. (standard deviation, 0.0065). However, the wide distribution and variation within the groups show that this slight difference is of little statistical significance (critical ratio, 0.89).

The mean value for women is 0.0214 sq. mm. (standard deviation, 0.0095), and that for men is 0.0203 sq. mm. (standard deviation, 0.0064). The ranges of distribution for men and women are essentially the same. The difference in mean values is too small to be of any significance.

The differentiations under the heading "Habitus" in table 1 were made after careful examination. Only those cases were designated as instances of pyknic or asthenic habitus which were unequivocal examples of the kretschmerian type. Those in which the distinctive features were not clear were classified as cases of undifferentiated type. We fully understand the limitations in such a method, but since our objective was to determine any difference between the two groups it was thought even safer to select only extreme types for comparison.[10] The mean value for cases of the pyknic type was 0.0199 sq. mm. (standard deviation, 0.0235), while that for cases of the asthenic type was 0.0214 sq. mm. (standard deviation, 0.0084). This difference is definitely not significant (critical ratio, 0.005). The German students of constitution have claimed that the retinal vessels in persons of the pyknic type are larger than those in persons of the asthenic type.[11] They have stated that this is representative of a general plethoric vascular system in the pyknic person. Their opinions are based on subjective impressions after ophthalmoscopic examination. Our figures definitely show that the size of the vessels of the fundus is not related to the asthenic or the pyknic habitus of the subject.

As we examined the columns headed "Duration" and "Clinical Status" in table 1, we were struck by the fact that there is a definite tendency for the cases of psychoses of longer duration to fall in the upper half of the table. Also, cases in which there is deterioration

10. The condition in one case listed as dysplastic was a pituitary anomaly similar to acromegaly, while in the other there was bilateral congenital dislocation of the hip.

11. Scherer, R.: Constitution and Blood Vessels of the Fundus, Klin. Monatsbl. f. Augenh. **97**:602, 1936.

show a definite tendency to group themselves on the basis of a smaller retinal vascular bed. In like manner, in cases in which improvement is increasing there is a tendency to much larger vessels.

All our manic-depressive patients are either improving or have recovered. When we remove cases of this type from the table, leaving only the cases of schizophrenia, the tendency for the cases to group themselves on the basis of outcome becomes even more apparent (table 2). If we arbitrarily select 0.0200 as a dividing line, then of 10 cases below this point deterioration is shown in 8, while of 8 cases

TABLE 2.—*Relation of Clinical Status to Size of Retinal Vascular Bed in Patients with Schizophrenia*

Sex	Age, Yr.	Retinal Vascular Bed, Sq. Mm.	Diagnosis	Duration, Mo.	Habitus	Clinical Status
F	24	0.0104	Catatonic-hebephrenic schizophrenia	45	Pyknic	Deteriorated
M	19	0.0148	Hebephrenic schizophrenia....	36	Undifferentiated	Deteriorated
M	21	0.0152	Simple schizophrenia.....	24	Undifferentiated	Deteriorated
F	17	0.0163	Hebephrenic schizophrenia....	42	Pyknic	Deteriorated
M	31	0.0166	Hebephrenic schizophrenia....	24	Pyknic	Circumscribed improvement
F	27	0.0174	Catatonic schizophrenia.....	6	Asthenic	Marked improvement
M	16	0.0181	Hebephrenic schizophrenia....	30	Asthenic	Circumscribed improvement
M	22	0.0185	Hebephrenic schizophrenia....	48	Asthenic	Improving
M	33	0.0193	Paranoid schizophrenia.....	54	Dysplastic	Circumscribed improvement
M	24	0.0194	Paranoid schizophrenia.....	4	Pyknic	Deteriorated
F	23	0.0207	Catatonic schizophrenia.....	8	Pyknic	Circumscribed improvement
F	20	0.0208	Catatonic schizophrenia.....	8	Asthenic	Improving
M	19	0.0226	Simple schizophrenia.....	10	Undifferentiated	Improving
M	18	0.0230	Hebephrenic schizophrenia....	60	Asthenic	Deteriorated
F	21	0.0231	Catatonic schizophrenia.....	4	Undifferentiated	Marked improvement
M	31	0.0254	Catatonic schizophrenia.....	8	Asthenic	Marked improvement
M	29	0.0258	Paranoid schizophrenia.....	8	Undifferentiated	Unimproved
F	20	0.0285	Hebephrenic schizophrenia....	11	Asthenic	Improving

above this line improvement is shown in 5. The mean value for the cases in which there is deterioration is 0.0174 sq. mm. The mean for the cases in which the condition is improving or markedly improved is 0.0223 sq. mm. The critical ratio of 2.45 between these two values points to the full significance of the difference.

We have already mentioned our interest in establishing the retinal vascular bed as an index of the vascular constitution. If we may assume such an attitude toward our measurements, it becomes obvious that this index must be corrected for differences in stature and body mass. In other words, it is to be expected that a man 6 feet (183 cm.) tall and weighing 200 pounds (90.7 Kg.) will normally have larger vessels than a woman 5 feet (152 cm.) tall and weighing 110 pounds (49.9 Kg.).

We have considered many possible corrections for this error, and after due deliberation it was decided to use the body volume. We realize that the vascular demands of various tissues are not dependent on volume alone, but in order to make allowances for the large variation in stature it seemed wise to allow the smaller error introduced by the different proportions of various types of tissue in different persons. Total body volume is most conveniently expressed as body weight.[12] Accordingly, we divided the vascular bed of the retina by the body weight, expressed in kilograms. The result was multiplied by 10,000 in order to give a

TABLE 3.—*Relation of Amount of Retinal Vascular Bed per Kilogram of Body Weight to Clinical Status of Patients with Schizophrenia*

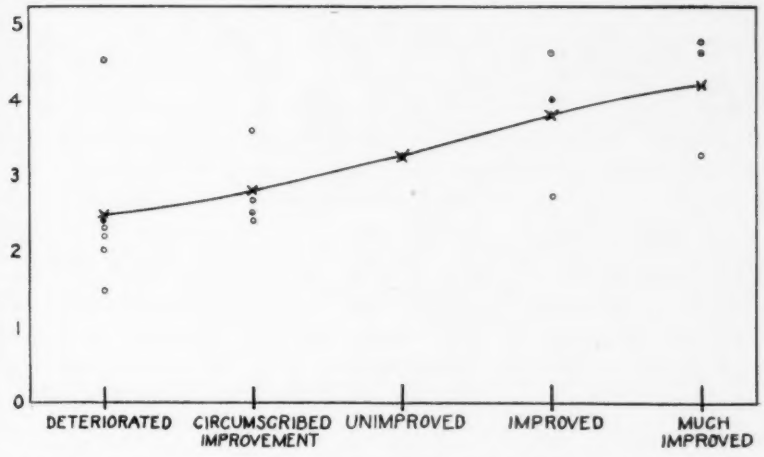
Sex	Age, Yr.	Retinal Vascular Bed, per Kg.	Diagnosis	Duration, Mo.	Habitus	Clinical Status
F	24	1.46	Catatonic-hebephrenic schizophrenia	45	Pyknic	Deteriorated
M	24	2.01	Paranoid schizophrenia	4	Pyknic	Deteriorated
M	21	2.21	Simple schizophrenia	24	Undifferentiated	Deteriorated
F	17	2.34	Hebephrenic schizophrenia	42	Pyknic	Deteriorated
M	19	2.37	Hebephrenic schizophrenia	36	Undifferentiated	Deteriorated
M	33	2.42	Paranoid schizophrenia	54	Dysplastic	Circumscribed improvement
M	31	2.52	Hebephrenic schizophrenia	24	Pyknic	Circumscribed improvement
M	16	2.68	Hebephrenic schizophrenia	30	Asthenic	Circumscribed improvement
M	22	2.72	Hebephrenic schizophrenia	48	Asthenic	Improving
M	20	3.25	Paranoid schizophrenia	8	Undifferentiated	Unimproved
F	27	3.28	Catatonic schizophrenia	6	Asthenic	Marked improvement
F.	23	3.59	Catatonic schizophrenia	8	Pyknic	Circumscribed improvement
M	19	3.80	Simple schizophrenia	10	Undifferentiated	Improving
F	20	4.00	Catatonic schizophrenia	8	Asthenic	Improving
M	18	4.51	Hebephrenic schizophrenia	60	Asthenic	Deteriorated
F	20	4.62	Hebephrenic schizophrenia	11	Asthenic	Improving
M	31	4.62	Catatonic schizophrenia	8	Asthenic	Marked improvement
F	21	4.75	Catatonic schizophrenia	4	Undifferentiated	Marked improvement

convenient figure. Table 3 shows the patients rearranged according to the increasing size of this new index figure, which represents the amount of retinal vascular bed per kilogram of body weight. None of the relationships already mentioned changed significantly, except that pointed out in the two columns "Duration" and "Clinical Status." The tendency for the deteriorating patients to group themselves on the basis of the small vascular bed is even more marked. Improving or recovered schizophrenic patients group themselves on the basis of a large vascular bed. If 3.5 is assumed as the meridian, 5 of the 7 patients with values above this are improving, while 2 show deterioration. Only 2 of the

12. Boyd, E.: The Specific Gravity of the Human Body, Human Biol. **5**:646, 1933.

11 patients with values below this are improving, and 9 are deteriorated or show only circumscribed improvement. A graph of this tendency is presented in the accompanying figure. It has been determined statistically that the chances are less than 5 in 100 that such a grouping could result from chance alone.

As this is a preliminary report of a much larger project, we are not yet ready to comment on the significance of these findings. However, it seems safe to point out that provocative evidence has been accumulated to add to that already gathered which would point to the importance of the vascular system in mental disease. The tendency of the findings in this small group points toward a relationship between prognosis in schizophrenia and the capacity of the vascular bed.



Correlation of the capacity of the retinal vascular bed and the clinical status of schizophrenic patients.

We fully realize the desirability of a larger group before definite conclusions can be drawn. We realize also that studies on prognosis are possible only after long periods of observation. We shall endeavor to overcome both of these objections by wide expansion of this research with careful follow-up contact with all patients.

SUMMARY

The cross-sectional area of the vascular bed of the retina has been measured in a group of psychiatric patients classified as having either schizophrenia or manic-depressive psychosis. It is believed that these measurements are an index of the developmental status of the general vascular constitution of the patient.

There is no correlation between the capacity of the retinal vascular bed and either of the two diseases studied. Contrary to previous impression, no correlation was found between habitus in the kretschmerian sense and the capacity of the vascular bed.

In the schizophrenic group there was a high degree of correlation between the clinical status of the patient and the capacity of the retinal vascular bed. Patients who do not improve or who deteriorate have a small retinal vascular bed in a high percentage of cases. Patients who improve or recover have a significantly larger vascular bed. When the measurements of the vascular bed are corrected for differences in stature in the group, the correlation between clinical status and the size of the vascular bed becomes even more significant.

PRIMARY INTRACRANIAL SARCOMAS

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The structural peculiarities of intracranial sarcomatous tumors were discussed by Bailey [1] in 1929 and again, with Bucy,[2] in 1931. Nevertheless, that the conclusions of those articles have not been thoroughly grasped by pathologists is evidenced by the fact that among the tumors sent to this clinic for differential diagnosis there is an unusually large percentage of sarcomatous tumors. For this reason it seems worth while to discuss this question further.

The term sarcoma in its original sense means only a fleshy tumor. In this sense the number of sarcomas in the brain is great, and this fact is reflected in the older literature. But when the term sarcoma was restricted to malignant tumors of mesodermal origin, pathologists became aware that most of the tumors of the brain no longer belonged in this category, and the diagnosis "sarcoma of the brain" almost disappeared. Newer studies of the finer microscopic structure of tumors of the brain made it apparent, however, that a few rapidly growing tumors were not of neuroglial origin and could adequately be accounted for only by supposing that they arose from the leptomeningeal tissue either over the surface of the brain or around the blood vessels within its substance.

However, at this point the applicability of the term sarcoma was again called into question by the theories of origin of the leptomeninges from the neural crest (Harvey and Burr,[3] Oberling [4]). These authors maintained that the leptomeninges are derived from the same source as the Schwann cells of the peripheral nerves and began to speak of the neurinomas as peripheral gliomas. In support of their theory they

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1. Bailey, P.: Intracranial Sarcomatous Tumors of Leptomeningeal Origin, Arch. Surg. **18**:1359 (April) 1929.

2. Bailey, P., and Bucy, P. C.: The Origin and Nature of Meningeal Tumors, Am. J. Cancer **15**:15, 1931.

3. Harvey, S. C., and Burr, H. S.: The Development of the Meninges, Arch. Neurol. & Psychiat. **15**:545 (May) 1926.

4. Oberling, C.: Les tumeurs méningées, Bull. Assoc. franç. p. l'étude du cancer **11**:365, 1922.

pointed not only to embryologic studies but also to the frequent association of meningeal tumors with the peripheral manifestations of Recklinghausen's disease and to the presence in the leptomeninges of melanoblasts. The weaknesses of this theory have been discussed by Bailey and Herrmann.[5]

Whatever the origin of the cells of the leptomeninges, the tumors arising from this tissue reproduce the structure of mesodermal tumors elsewhere (Penfield[6]). The mesenchyme of the head region, nevertheless, has a double origin, as embryologists have shown (Stone[7]), and this accounts for the presence of melanophores which sometimes give rise to melanoblastomas of the leptomeninges.[8] This leptomeningeal tissue, arising from the mesenchyme of the head region, is the only source for sarcomatous tumors within the brain, with the exception of the endothelium of the blood vessels, the white blood corpuscles and the microglia. The leptomeningeal tissue permeates the brain around every blood vessel at least as far as the true capillaries (Schaltenbrand and Bailey[9]). Recently a few reports have claimed the microglial origin of tumors of the brain (Yuile,[10] Awzen[11]). However, the interpretation of the silver impregnations on which such conclusions are based is doubtful. Del Río Hortega and Jimenez de Asúa[12] long ago showed that macrophages from any source will be impregnated by the technic for microglia, and the presence of numerous macrophages in tumors of the brain was proved by Penfield.[13] Such intracranial tumors would in any case be mesodermal, since the microglia is of mesodermal origin. There being no adequate evidence that the

5. Bailey, P., and Herrmann, J. D.: The Rôle of the Cells of Schwann in the Formation of Tumors of the Peripheral Nerves, Am. J. Path. **14**:1, 1938.

6. Penfield, W.: The Encapsulated Tumors of the Nervous System, Surg., Gynec. & Obst. **45**:178, 1927.

7. Stone, L. S.: Experiments Showing the Rôle of Migrating Neural Crest (Mesectoderm) in the Formation of Head Skeleton and Loose Connective Tissue in Rana Palustris, Arch. f. Entwcklngsmechn. d. Organ. **118**:40, 1929.

8. Schnitker, M. T., and Ayer, D.: The Primary Melanomas of the Leptomeninges, J. Nerv. & Ment. Dis. **87**:47, 1938.

9. Schaltenbrand, G., and Bailey, P.: Das perivasculäre Piagliamembran des Gehirns, J. f. Psychol. u. Neurol. **35**:199, 1928.

10. Yuile, C. L.: Case of Primary Reticulum Cell Sarcoma of the Brain: Relationship of Microglia Cells to Histiocytes, Arch. Path. **26**:1036 (Nov.) 1938.

11. Awzen, A. P.: Du type spécial des tumeurs mésenchymes non mûries du système nerveux central (un cas de mésoglioblastome), Acta med. Scandinav. **87**:470, 1936.

12. del Río Hortega, P., and Jimenez de Asúa, F.: Sobre la fagocitosis en los tumores y en otros procesos patológicos, Arch. de cardiol. y hematol. **2**:161, 1921.

13. Penfield, W.: Microglia and the Process of Phagocytosis in Gliomas, Am. J. Path. **1**:77, 1925.

microglia, the white blood corpuscles or the endothelium of the blood vessels plays any role in the formation of tumors, it is conceived that primary tumors in the brain which reproduce the structure of sarcomas elsewhere in the body must arise from the leptomeningeal tissue either over the surface of the brain or around its blood vessels. It will be seen later that the site of origin accounts for certain peculiarities of these tumors.

All the intracranial sarcomatous tumors are rapid growing, with numerous mitotic figures, and, although they do not, in my experience, metastasize outside the intracranial cavity, they do spread widely along the leptomeningeal or perivascular spaces, are not encapsulated and are rapidly destructive to the neural parenchyma. They form the usual intercellular fibrillary structures of connective tissue in varying abundance. Although few, only about 60 cases being recognizable in the literature, their rarity is doubtless exaggerated by the fact that they are often not diagnosed.

These tumors, in my experience, have been of four types. I shall describe a case of each type in detail.

REPORT OF CASES

SARCOMATOSIS OF THE MENINGES

CASE 1.—L. J., a girl aged 19 years, was admitted to the University of Chicago Clinics on Oct. 29, 1931, with the chief complaints of severe headaches and vomiting for two months and double vision for seven weeks. She was referred by Dr. Peter Bassoe, of Chicago.

History.—The family had observed that she held her work close to her eyes for several months; she attributed this to habit when her attention was directed to it. When climbing Starved Rock in May, she struck her head on a projection of rock, fell to the ground, striking her hip, and was dazed for a few seconds. While a councilor at camp in August, she fell on her head. She was dazed only for a moment. Later in August she awoke in the middle of the night, was nauseated and vomited. About Labor Day she became nauseated at school and had to lie down all day. After this she began to have severe headaches on arising in the morning, vomited and was unable to attend school. The headaches began when she raised her head from the pillow and were soon followed by projectile vomiting. At first she was free from these symptoms from two to three days a week, but later her condition became progressively worse and she had been confined to bed during the last month. She began then to see double and was found to have weakness of the left side of the face.

Examination.—She complained of headache in the middle occipital region when she sat up, and it became worse when the head was percussed. She had to lie on her right side to prevent pain and nausea. There was some limitation in flexion of the neck anteriorly. Blinking of the right eye was increased. The left palpebral fissure was larger than the right. There was occasional coarse nystagmus to the left. Convergence was impossible; the left eye moved slightly but the right eye not at all. Conjugate movement to the right side could not be maintained. The optic disks were distinctly hyperemic and their margins slightly swollen.

Flame-shaped hemorrhages were present in the left disk. Diplopia due to paresis of the left internal and superior rectus muscles was present. The left facial muscles were weak. There was definite increase in tone of the right upper extremity. The outstretched right arm drooped and deviated laterally. The left abdominal muscles moved more vigorously than the right. Extension and flexion of the thighs were not well performed. The tone of both legs was diminished. The knee jerk was greater on the right. The left ankle jerk was greater than the right. A roentgenogram of the skull revealed nothing abnormal. Laboratory findings were not remarkable. The clinical diagnosis was tumor in the posterior fossa, probably pontomedullary.

Operation.—With the patient under ether anesthesia, Dr. Percival Bailey made exploration on Nov. 3, 1931. The bone and dura mater in the suboccipital region were tense. The lateral ventricle was punctured to reduce tension. When the dura mater was opened the posterior cistern was observed to be filled with a soft, reddish gray matter of tumor. This spread out also underneath the arachnoid membrane over the surface of the right hemisphere. The median mass extended down through the foramen magnum and could not be displaced upward. The capsule of the tumor was removed piecemeal. The tumor was followed upward until the fourth ventricle was opened. The medulla oblongata was observed to be pushed to the left and flattened laterally. A considerable mass of the tumor was removed from the right angle, but its complete removal was impossible because it involved nerves in this region and there was smart bleeding.

Surgical Specimen.—The tumor was composed of spindle cells forming considerable intercellular fibrillary material of connective tissue nature. The nuclei were vesicular and crenated. There were many mitoses. The pathologic diagnosis was sarcoma of the meninges.

Subsequent Course.—About thirty-six hours after operation the patient became comatose and began to have respiratory difficulty. Puncture of the lateral ventricles failed to give her relief. With local anesthesia, a midline incision was made in the suboccipital region. The atlas and axis were removed, and the dura mater was opened down to the third cervical vertebra. The patient's condition remained poor, and she died on Nov. 5, 1931.

Necropsy.—An examination was made twelve hours post mortem by Dr. E. M. Humphreys. The general necropsy observations were: slight hydrothorax on the left, petechial hemorrhages in the left visceral pleura, encapsulated caseocalcareous tubercles in the right hilus and peribronchial lymph nodes and supernumerary cusps of the pulmonary valve.

The leptomeninges about the bulb in both cerebellopontile angles were diffusely infiltrated with grayish tumor, which extended forward to the optic chiasm. Median sagittal sections of the brain showed that the tumor had involved the meninges throughout the basilar cistern and had extended up between the frontal lobes. It had also completely surrounded the brain stem at the midbrain and was visible above the anterior medullary velum and over the corpora quadrigemina to the pineal body. The leptomeninges of the spinal cord were infiltrated with tumor into the cauda equina, where there were nodules about 1 cm. in diameter. The tumor was mostly present on the dorsal surface of the cord, although there were some nodules in the meninges on the ventral surface.

Microscopic Examination.—The tissue presented structures of two types. In some areas the structure and arrangement of the neoplastic cells resembled those of meningioma of the fibroblastic and meningotheliomatous types. Some cells were arranged in whorls, others in parallel bands. The cells were either oval or spindle

shaped. The nuclei were elongated or oval and vesicular. The nuclear membrane was distinct and occasionally crenated. The cytoplasm of the spindle-shaped cells was moderately rich and showed distinctly the fine fibrils. There were no giant cells. In other areas the cells lay in compact masses without showing any definite pattern. They were moderate in size and elongated, oval or polygonal. They had little cytoplasm. Intercellular fibrils were abundant. Most of the nuclei were vesicular and tended to be of irregular shape. In many places the cells extended into the superficial layers of the cortex along the perivascular spaces of the pial blood vessels. They were usually confined there without breaking through the pia-glial membrane, but in several places the pia mater was ruptured, allowing the tumor cells to spread directly into the cerebral tissue (fig. 1 *A*). Numerous mitotic figures were noticed throughout the tumor tissue. Impregnation by Perdrau's method revealed an abundant network of fine reticulin fibrils along the tumor cells, often more distinct around the blood vessels. Most of the tissue, however, had been discarded or lost, and, with the limited material at my disposal, although Perdrau preparations good enough for microscopic study could be obtained, they were not clear enough to photograph well. For that reason, I have added a photograph from a similar case (fig. 1 *B*) which gives an adequate impression of the distribution of the reticulin in cases of sarcomatosis.

Beyond doubt this tumor arose in the leptomeninges, and in places formed the whorls typical of the usual meningotheliomatous tumors. Its widespread distribution and occasional invasive tendencies, however, differentiate it from the usual bulbous meningioma and justify one in speaking of sarcomatosis of the meninges. The tumor cells contained no melanin, and their structure was quite different from that of a medulloblastoma. A complete necropsy did not reveal evidence of tumor outside the leptomeningeal spaces.

Reports of tumors of this type are numerous in the literature. Typical examples have been described by Greenfield,[14] Connor and Cushing,[15] Bailey [1] and Bailey and Bucy [2] among many others. In this clinic more than a dozen cases of such tumors have been observed. In many such cases the neoplastic cells remain confined to the perivascular spaces (fig. 8 *A*), but in many instances they may break out of the perivascular spaces (fig. 9 *B*) or invade the brain directly through the pia mater (fig. 9 *A*).

ALVEOLAR SARCOMAS

CASE 2.—M. B., an unmarried woman aged 26, was admitted to the University of Chicago Clinics on March 12, 1931. She was referred by Dr. G. W. Hall, of Chicago.

History.—For the past eight years she had at times had frontal headaches. A physician said her eyes were weak, and she secured glasses. She was then well until within seven weeks before admission, when she began to experience severe

14. Greenfield, J. A.: The Pathological Examination of Forty Intracranial Neoplasms, Brain **42**:29, 1919.

15. Connor, C. L., and Cushing, H.: Diffuse Tumors of the Leptomeninges: Two Cases in Which Process Was Revealed Only by the Microscope, Arch. Path. **3**:374 (March) 1927.

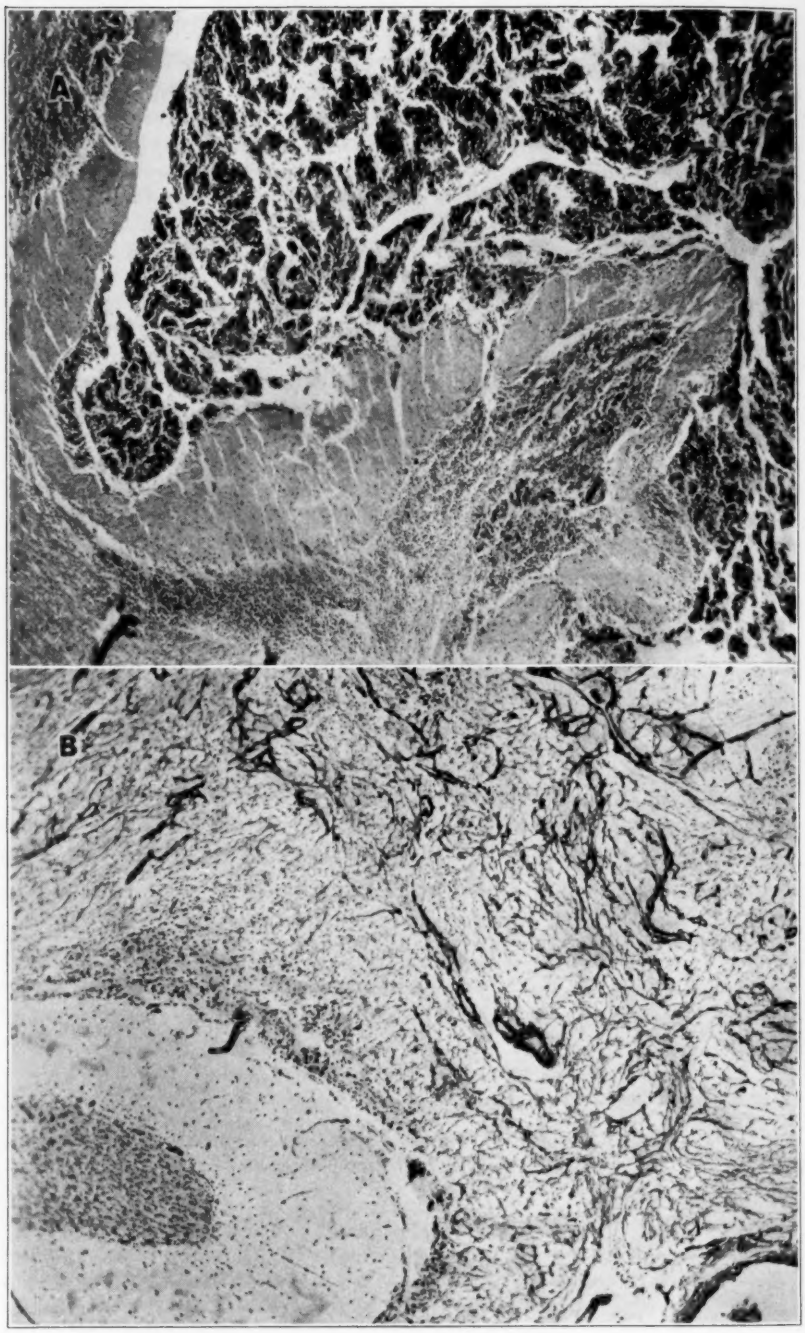

Fig. 1.—*A* (case 1), hematoxylin and eosin; × 45. Diffuse infiltration of the subarachnoid space with the neoplastic cells. *B*, Perdrau's method; × 45. Strands of reticulin permeating neoplastic tissue in a case of sarcomatosis.

headaches, dizziness and unsteadiness. On walking she tended to fall to the right side. Headaches were localized in the frontal region. Soon after the onset of the present illness she vomited repeatedly, without nausea. She was unable to lie on her right side because this position caused dizziness and vomiting. Lying on her back caused headaches in the back of her skull. She had lost 17 pounds (7.7 Kg.) in weight.

Examination.—On admission the patient seemed acutely ill. There was definite tenderness over the right occipital region of the skull and around the region of the foramen magnum. The head was rotated to the left. On motion of the head she complained of pain in the nape of the neck. There was early papilledema on both sides, slightly more marked on the right than on the left. There was variable nystagmus. She had slight weakness of the right facial nerve of peripheral type and deviation of the jaws to the right when the mouth was opened. On extension of the arms there was coarse tremor of the hands, which was inconstant and inconsistent. The right arm was uncertain, and the right leg had a definite intention tremor. Visual fields were normal. Vestibular tests gave normal results in spite of the dizziness. A roentgenogram of the skull did not reveal any definite abnormality. The positive findings were all indefinite and variable. A diagnosis of intracranial tumor, probably in the fourth ventricle, was made.

Operation.—With local anesthesia, Dr. Percival Bailey operated on March 17, 1931. The cerebellar tonsils were slightly herniated into the foramen magnum. No tumor in the fourth ventricle could be seen. Puncture of the hemispheres with an exploring needle revealed a firm tumor at a depth of about 1 cm. The posterior portion of the vermis was split longitudinally, the knife coming down on the surface of a circumscribed tumor. The cerebellum was dissected free from the growth on both sides, and the tumor was followed posteriorly to the fourth ventricle. It was obviously too large to shell out; so it was removed piecemeal with the electric loop.

Surgical Specimen.—The tissue was composed of closely packed cells with oval nuclei. There were numerous mitotic figures and fine reticulin fibrils.

Subsequent Course.—The postoperative course was uneventful. Intensive roentgen treatment over the whole cerebrospinal system was started on April 8 and completed on April 20, 1931. The patient was discharged on April 21, much improved. However, she continued to have vomiting spells from time to time. Because of repeated attacks of pain in the epigastrium since June, she was readmitted to the hospital on Oct. 11, 1931. The positive findings at this time were pain and tenderness over the epigastrium and slight jaundice, with an icteric index of 22.2. Roentgen examination showed nonvisualization of the gallbladder after intravenous administration of dye. Because of the impression of chronic cholecystitis and cholelithiasis, operation was performed on Oct. 16, and one small stone in the cystic duct was removed. The following neurologic signs were noted: indistinctness of the nasal sides of the disks, narrowing of the right palpebral fissure and slight nystagmus and slight deviation of the jaw to the right. A second series of roentgen treatments over the whole cerebrospinal system was begun on October 26 and completed on November 3. She was discharged on November 6. After discharge she had almost constant headaches, daily vomiting, pain in the eyes, repeated attacks of swelling over the left lower occipital region and constipation. She was taken into the hospital for the third time on June 26, 1932, and was given another series of roentgen treatments. During her stay in the hospital, up to Feb. 4, 1932, she presented no new neurologic findings except slight ataxia of the left arm and a small amount of bulging in the region of the suboccipital decompression.

In the outpatient department, she was given further courses of roentgen therapy, one in May 1932 and the other in September.

Except for occasional vomiting, she remained well until Dec. 5, 1932, when she again noticed swelling and pain over the left suboccipital region and headaches, for which she entered the hospital for the fourth time. Neurologic examination revealed inequality of the pupils, the right being larger than the left, slight limitation of conjugate movement to the right; coarse slow nystagmus on looking to the right; weakness of the lower left side of the face; deviation of the uvula to the right during rest; generalized hypotonia, most marked in the right arm; marked ataxia on both sides, especially in the right hand; walking on a broad base and staggering to the right; tenderness and bulging of the suboccipital region; slight turning of the head to the left during rest; slightly exaggerated tendon reflexes, and a Babinski sign bilaterally. The sixth series of roentgen treatments was begun on Dec. 19, 1932. In all, about 12,000 roentgen units had been given to all parts of the central nervous system. Ventricular puncture was made on Dec. 20. A second operation was performed on Jan. 3, 1933. The old wound was opened, and a subarachnoid cyst, containing a few cubic centimeters of fluid, was observed. The entire central body of the cerebellum was occupied by a large, soft, grayish red tumor, a large part of which was removed.

Surgical Specimen.—One block consisted of sclerosed cerebellar cortex, with some tumor infiltrating the meninges. The other block was of tumor, much infiltrated with blood. The nuclei were vesicular and varied much in size. There were many mitoses. The reticulin fibers radiated around the numerous blood vessels. The diagnosis was sarcoma.

Subsequent Course.—The patient was finally discharged on Jan. 25, 1933. After that her condition became progressively worse, and she died at home on April, 13, 1933.

Necropsy.—An examination, limited to the head and spine, was made by Dr. J. D. Stewart, after the body had been embalmed. The skin over the suboccipital region was thickened but not bulging. The muscles were infiltrated with tumor. The dura mater in the region was likewise infiltrated, but over the hemispheres it was normal. The cerebral hemispheres showed slight flattening of the convolutions, but no hyperemia or thickening of the meninges. The cerebellum was involved by the extensive tumor, mainly on the right side. The brain stem was shifted markedly to the left. The tumor on section appeared to be composed of two types of tissues, one white and of rubbery consistency, the other softened and stained with blood and various blood pigments. All the ventricles were dilated. The arachnoid membrane over the spinal cord was possibly slightly thickened; otherwise, the cord was normal.

Microscopic Examination.—The tissue was very cellular and in places resembled the embryonic mesenchyme. Foci of necrosis of various degrees were present, but showed no definite spatial relationship to the blood vessels. Some of these necrotic foci had been replaced by dense strands of collagen. The preserved neoplastic cells were divided into distinct alveoli by a connective tissue stroma. The tissue was composed of vesicular, elongated, oval or irregular nuclei and fine fibrils. Its cellularity and compactness varied from place to place (fig. 2 *A*). The cells in the alveoli were irregular in shape and size. Most of them were oval, some slightly elongated and a few rounded. In general the cells in the alveoli did not differ much from those in the stroma. There were numerous mitotic figures. No capsule was formed about the tumor. Impregnation by Perdrau's

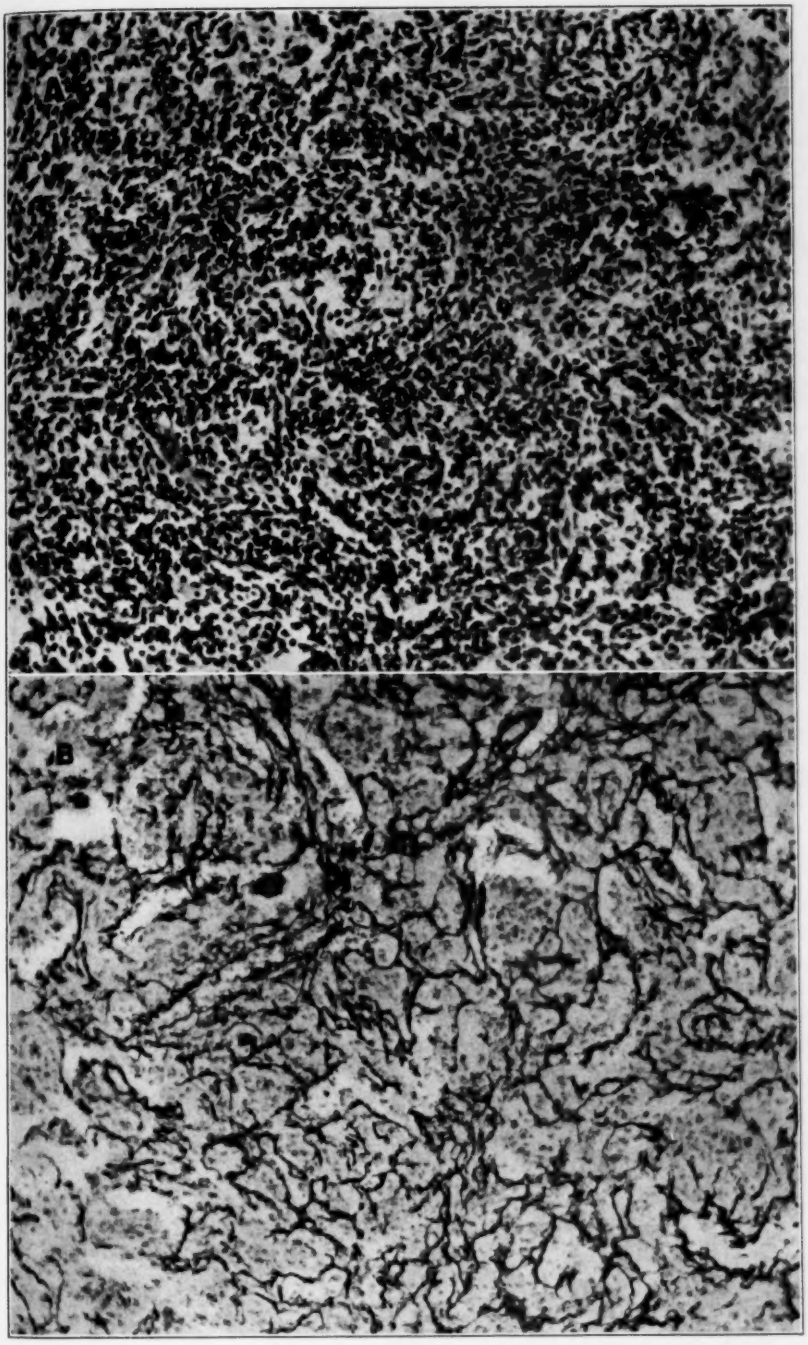

Fig. 2 (case 2).—*A*, hematoxylin and eosin; × 150. Alveolar arrangement of the neoplastic cells. *B*, Perdrau's method; × 150. Alveolar distribution of the reticulin fibrils.

method showed fine strands of reticulin arranged in an alveolar network throughout the tissue (fig. 2*B*). The pathologic diagnosis was alveolar sarcoma.

The mesenchymal appearance, the connective tissue stroma, not distinct from the neoplastic cells, and the formation of reticulin leave no doubt that the tumor was of connective tissue nature. The slight variation in microscopic appearance of the tissue removed at biopsy and of that seen at necropsy was insignificant and could be explained by the normal variability in various parts of any tumor, or possibly by the roentgen treatment. The latter explanation is not likely, however, since the treatments were spread over almost two years. The differences between the cells of the stroma and those of the alveoli may be found in any sarcoma of this type anywhere in the body (Speciale,[16] Romano [17]).

The differentiation of these tumors from medulloblastomas has been discussed by Bailey, Buchanan and Bucy.[18] In addition to the differences in microscopic structure, one may point out that the patient was beyond the usual age at which medulloblastomas occur.

FIBROSARCOMA

CASE 3.—G. L. I., a laborer aged 27, was first admitted to the University of Chicago Clinics on Sept. 23, 1935. He was referred by Dr. L. F. Waldmann, of Waukegan, Ill.

History.—The patient had had headache since Jan. 2, 1934, which was thought to be due to frontal sinusitis. On June 12, 1935, three days after a bilateral intranasal operation, vision of the right eye was lost. Vision of the left eye was affected at the same time, but cleared until September 9, when he again suffered sudden reduction of vision in the left eye. Both fundi showed hemorrhages and papilledema. The process in the left eye was acute, while that in the right was accompanied by atrophy. The other definite finding was loss of position and vibratory sense in the left hand. A roentgenogram of the skull revealed clouding of the right ethmoid cells and the right maxillary and left frontal sinuses and erosion of the posterior clinoid processes and floor of the sella turcica. On Oct. 2, 1935, puncture of the right parietal lobe revealed a cavity at a depth of 6 cm., from which yellowish fluid under pressure escaped. Air was injected into the cavity. Roentgen examination showed a cyst in the right parietal region. The sella turcica was secondarily eroded. The clinical impression was that of cystic glioma of the right parietal lobe.

On Oct. 7, 1935, the additional neurologic findings were: slight weakness of the musculature of the left side of the face, impairment of touch and pain sensation and exaggeration of ankle and knee jerks on the left side.

Operation.—On Oct. 8, 1935, an osteoplastic craniotomy was done by Dr. Percival Bailey. The cortex of the right parietal region was flattened and rather

16. Speciale, F.: Il tessuto reticulare nei tumori, Tumori **10**:37, 1923-1924.

17. Romano, G.: Il sistema delle gitterfasern con speciale riguardo al loro sviluppo nei tumori, Tumori **2**:119, 1912.

18. Bailey, P.; Buchanan, D. N., and Bucy, P. C.: Intracranial Tumors of Infancy and Childhood, Chicago, University of Chicago Press, 1939.

avascular. A large area of cortex overlying the cyst, together with a mass of tumor, was removed.

Surgical Specimen.—The tumor was composed of cells having abundant cytoplasm. Most of them were spindle shaped, with elongated, irregularly shaped, crenated nuclei. There were many multinucleated cells and fat-laden macrophages. Lymphocytes were also seen. In some areas there was rather abundant reticulin. There was no definite capsule, although the margin was fairly sharp. Some areas were necrotic. One mitosis was found. The pathologic diagnosis was meningeal tumor of unusual structure.

Subsequent Course.—The postoperative course was uneventful, and the patient was discharged on October 19. On Nov. 15, 1935, he was seen again in the ophthalmologic service. Vision of the right eye was completely gone, while the left eye could perceive only light. On Jan. 18, 1937, he was readmitted to the hospital on account of headaches of increasing intensity for two weeks and numbness of the left hand for one week. Since the last operation he had felt well except for occasional headache. Recently the headaches had become severe and constant, and he noticed tenderness and bulging over the region of the right temporal decompression. Numbness of the left hand was annoying. He vomited several times. The positive neurologic findings by this time consisted of loss of sense of smell on both sides; complete blindness of both eyes, with secondary optic atrophy and papilledema of 2 D.; impairment of both motor and sensory components of the left trigeminal nerve; slight weakness of the lower left side of the face; weak pharyngeal reflex on the left and weakness of the left sternocleidomastoid muscle; hemianesthesia on the left side, and slight increase of muscle tone with increase in tendon reflexes and absence of abdominal reflexes on the left side. No Babinski sign could be elicited. Because of the impression of recurring tumor, the patient was operated on by Dr. Percival Bailey for the second time on Jan. 21, 1937.

Second Operation.—The well healed old wound was opened. A diffuse infiltrating tumor filled the entire parietotemporal region. There was no cystic cavity of any great size. An irregular mass of tumor was removed.

Surgical Specimen.—The tumor tissue was impinging on the sclerotic cerebral cortex. It was cellular, and the cells were arranged in whorls and parallel bands. The compactness of the cells varied from one region to another. There were a few foci of necrosis, of which some had macrophages and lymphocytes and some were replaced by collagen. The blood vessels, especially in the neighborhood of such foci, were heavily infiltrated with small round cells. The shape, size and staining properties of the cells varied considerably. Spindle or ovoid cells predominated (fig. 3*A*). There were, in addition, bizarre forms. Some cells were almost twice as large as others. On the whole the nuclei were large, elongated and vesicular. The nuclear membranes were distinct, some being smooth and some crenated. In the cytoplasm of the spindle-shaped cells, the bipolar processes of which extended a variable distance, one could see clearly numerous fine fibers. The bizarre forms had one or more eccentric nuclei, homogeneous cytoplasm and a few blunt processes. Vacuoles were numerous in the cytoplasm of such cells. These giant cells were more abundant in some areas than others. Mitotic figures were frequent. There was no capsule. The neoplastic cells advanced directly against the brain tissue. Impregnation by Perdrau's method revealed marked proliferation of reticulin fibrils among the tumor cells (fig. 3*B*). In certain areas they were more abundant and coarse, while in others, where the cells resembled mesenchyme, they were delicate and much less heavily impregnated.

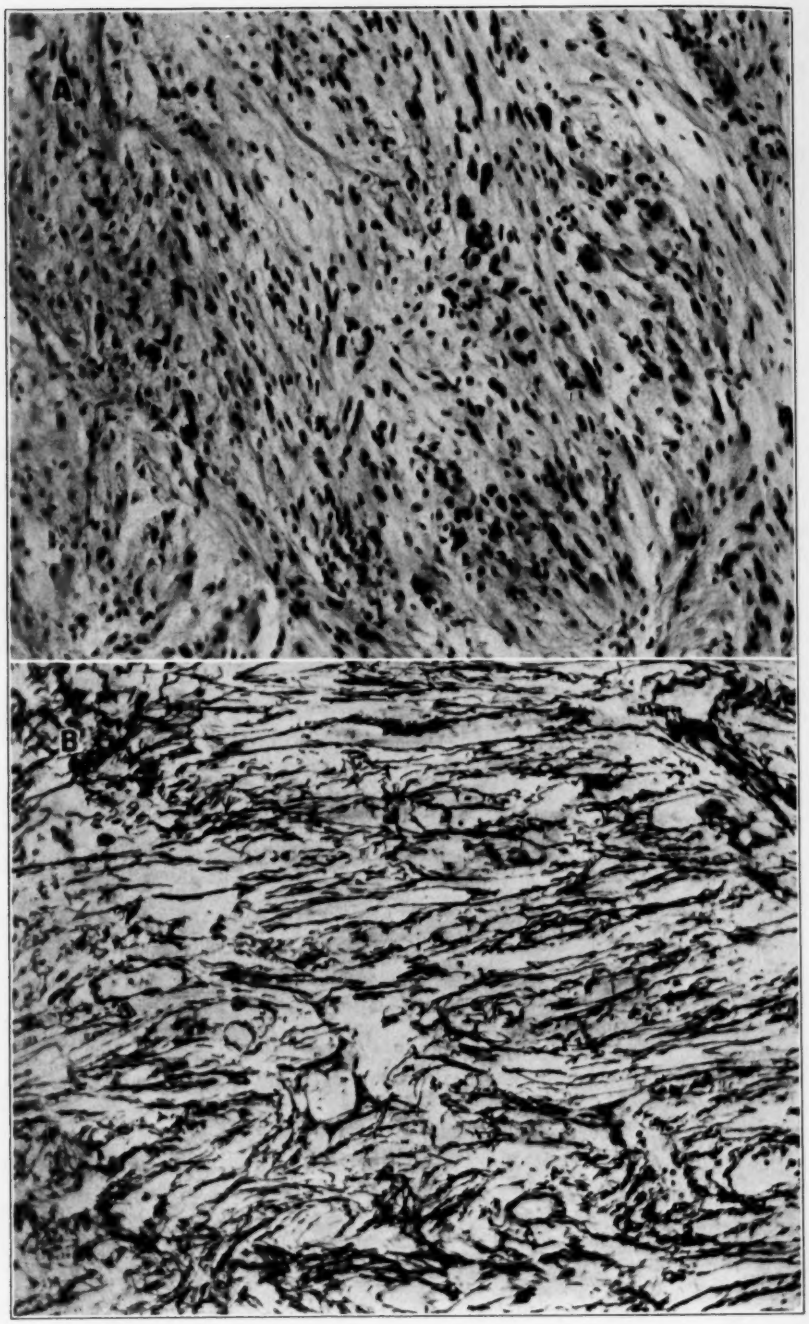

Fig. 3 (case 3).—*A*, hematoxylin and eosin; × 150. Spindle-shaped cells with distinct fibroglial fibrillae and many multinucleated cells. *B*, Perdrau's method; × 150. Parallel bands of the reticulin fibrils among the neoplastic cells.

Coarse masses of collagen were also noticed in several places. The pathologic diagnosis was fibrosarcoma of leptomeningeal origin.

Subsequent Course.—After the operation the patient was given high voltage roentgen radiation, of about 2,000 roentgen units, over the tumor. He was discharged on Feb. 14, 1937. He died at home on Nov. 6, 1938. Permission for necropsy was not obtained.

There was no obvious point of origin from the meninges, but the general microscopic appearance with formation of whorls suggested in many places the usual meningotheliomatous tumor. In other parts, however, the cells resembled those of fibrosarcomas elsewhere in the body. The amount of intercellular material formed by the neoplastic cells varied considerably. In areas with few mitoses a great deal of reticulin, with even masses of collagen, was formed. In other, more rapidly growing, areas the tissue resembled embryonic mesenchyme and formed delicate fibrils, difficult to impregnate. The giant cells were found in the neighborhood of degenerated areas. In these areas the appearance was much like that of the tumor reported by Foot and Cohen.[19]

Such a tumor could readily be confused with a glioblastoma. In glioblastomas there may be an abundant overgrowth of fibroblasts to organize degenerated areas. But in any such tumors areas of glial tissue can be readily found. In the present tumor no trace of glial tissue could be seen within the neoplastic mass. Its margin advanced in an irregular border against the brain tissue without leaving behind it enclosed masses of neural parenchyma.

Such primarily fibroblastic tumors within the brain are rare. Among probable cases in the literature, one may mention Cabot case 16,301 [20] and the cases of Zagni;[21] Foot and Cohen;[19] Bailey;[1] Alpers, Yaskin and Grant;[22] Armenise;[23] Balduzzi[24] and Foerster and Gagel.[25] The case here described is the only one of this type which I have personally observed.

PERITHELIAL SARCOMA

CASE 4.—R. P. A., a boy aged 9 years, entered the University of Chicago Clinics on March 3, 1939. He was referred by Dr. V. E. Lennarson, of Waukegan, Ill.

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19. Foot, N. C., and Cohen, S.: Report of a Case of Reticulo-Sarcoma of Cerebral Hemisphere, Am. J. Path. **9**:123, 1933.

20. Primary Fibrosarcoma of the Brain; Primary Carcinoma of the Pancreas, Cabot Case 16301, New England J. Med. **203**:174, 1930.

21. Zagni, L.: Sur deux cas de sarcome primitif des hémisphères cérébraux; contribution anatomopathologique et histogénétique, Néoplasmes **5**:159, 1926.

22. Alpers, B. J.; Yaskin, J. C., and Grant, F. C.: Primary Fibroblastoma of the Brain, Arch. Neurol. & Psychiat. **27**:270 (Feb.) 1932.

23. Armenise, P.: Un caso di sarcoma cerebrale, Cervello **11**:25, 1932.

24. Balduzzi, O.: Sarcoma magno-cellulare cerebrale primitivo, Riv. sper. di freniat. **62**:695, 1938.

25. Foerster, O., and Gagel, O.: Das umschriebene Arachnoidealsarkom des Kleinhirns, Ztschr. f. d. ges. Neurol. u. Psychiat. **164**:565, 1939.

History.—The boy was born one month prematurely, on July 11, 1930. His feeding and development were normal. He had the usual children's diseases, of which whooping cough was severe. On account of otitis media, he had had a myringotomy once a year for three or four years. He was otherwise well until Jan. 20, 1939. Since that time he had frequent attacks of headaches associated with vomiting and abdominal pain. He complained of dizziness, dimness of vision and diplopia for four weeks, and of diminution of memory and limitation of speech for a few days.

Examination.—When admitted, the patient was found to have bilateral weakness of the external rectus muscles, bilateral papilledema of 4 D., slight weakness of the lower facial muscles on the right side, unsteadiness of gait, rigidity of the neck and a suggestive Macewen's sign. A diagnosis of intracranial neoplasm was made. The location being doubtful, an encephalogram was made, which showed marked shift of the septum pellucidum to the right and downward displacement of the left ventricle.

Operation.—Under ether anesthesia, the boy was operated on by Dr. Percival Bailey on March 16, 1939. A bone flap was made in the left parietotemporal region. After incision of the tense dura mater, a tumor of the brain extending to the surface of the left angular gyrus was disclosed. It was not attached to the dura mater. An incision of the cortex was made, and a soft mass, about 5 cm. in diameter, was removed.

Surgical Specimen.—The tissue was composed mainly of areas of necrotic and dying cells, with islands of healthy cells. In these islands there were many blood vessels amid a dense mass of nuclei, about which almost no cytoplasm was present. There were many mitotic figures. Perdrau's method demonstrated scattered strands of reticulin extending from the vascular sinuses into the mass of tumor cells. Meningeal sarcoma was the pathologic diagnosis.

Subsequent Course.—Roentgen therapy was started on March 20, with a total dose of 2,138 roentgens in twenty-five days. After operation the patient had a high temperature and was irritable for a few days. He was discharged on April 22. He reappeared in the clinic on May 22, 1939 and, because of headache, was readmitted to the hospital on May 31. He was very ill and lethargic. The fundi showed secondary optic atrophy. There was a large, soft swelling over the temporal region. The tendon reflexes were exaggerated in the upper extremities and diminished in the lower. The patient died on June 29, 1939.

Necropsy.—Examination was made fourteen and a half hours post mortem by Dr. P. E. Steiner. A few cutaneous nevi were found, none of which showed any sign of activity. A small nodular mass was observed in the medulla of the left adrenal gland. It was a ganglioneuroma, with no evidence of activity. Grossly, the brain was asymmetric, the left cerebral hemisphere being much larger than the right and the latter being pushed considerably to the right. The convolutions were flattened throughout. The dura mater over the left temporal, parietal and occipital regions was thickened, rough and firmly adherent to the underlying brain tissue. There were a few small, discrete patches of yellowish tissue on the external surface of the dura mater. The meninges were otherwise not remarkable. The meningeal blood vessels in the exposed portion of the brain were essentially normal. Coronal sections showed that the cerebral white matter, particularly in the left frontal lobe, was tremendously edematous and had a yellowish green tint. From the level of the mamillary bodies in the left cerebral hemisphere a huge tumor extended over an area covering almost the whole superior temporal and great portions of the parietal and occipital regions. It involved not

only the white matter but also the cortex, especially on the lateral aspect. Laterally it was continuous with the thickened dura mater at the temporoparietal region. Medially, the insula and claustrum, the external and internal capsules, a portion of the corpus striatum and the body of the left lateral ventricle were also involved. The thalamus and hypothalamus were spared. As the tumor passed caudally, it stopped in the lateral half of the occipital lobe at a level 2 cm. from its pole. At its most extensive part it had a horizontal diameter of 7 cm. and a dorsoventral diameter of 7.5 cm. There was no definite capsule around the tumor, although it was usually well demarcated. In places the tumor tissue spread insensibly into the brain. It was fleshy, the consistency varying from soft and rubbery to friable. There were areas of necrosis, giving it a mottled appearance, with yellowish streaks, grayish stripes and dark red blood clots mixed irregularly. The lateral ventricles, as well as the structures at the midline, were pushed by the tumor to the right. Both the right lateral ventricle and the left temporal horn were dilated, the ependyma being rough and thickened. Small hemorrhages were noticed around the cerebellar nuclei. There was a moderate cerebellar pressure cone. The spinal cord was not available.

Microscopic Examination.—The neoplastic cells arranged themselves in irregular, compact masses. The nuclei were of moderate and fairly uniform size. They were rich in chromatin and irregular in outline and were mostly angulated. Such an angular appearance apparently resulted from the cells being packed closely against one another. There was no distinct cytoplasm. Mitoses were numerous. The blood vessels were thin and irregularly distributed. There were, however, blood vessels showing thickening of the walls with proliferation of cells which had nuclei more vesicular than those of the neoplastic cells. The neoplastic cells which were situated between the blood vessels had undergone necrosis (fig. 4 *A*), accompanied by macrophages and old and fresh hemorrhages. The degenerated neoplastic cells were smaller and more irregular in outline and stained more deeply than the other tumor cells. The necrotic foci varied in both extent and intensity. Their presence gave the preserved tumor cells around the blood vessels a pseudoperithelial appearance. No capsule of any sort could be demonstrated. The tumor cells advanced against the brain tissue by direct spreading more than by extension through perivascular spaces (fig. 8 *B*). Perdrau's method showed excellently an increase of reticulin fibers radiating around the blood vessels (fig. 4 *B*). In many places such fibrils were broken and irregularly scattered among the tumor cells.

Morphologically, the neoplastic cells in this tumor did not show features suggesting neuroglia. On the contrary, they were of the nature of connective tissue and must have originated from the perithelium of the blood vessels. This conclusion is substantiated by the close relationship of the neoplastic cells to the reticulin around the blood vessels. The absence of any appreciable amount of reticulin except in the immediate neighborhood of the vessels can be explained by the rapidity of growth and by the extensive intervascular necrosis. The nature of the neoplastic cells probably also played a role. Certainly, the cells did not resemble fibroblasts. I have recently observed a similar, but less malignant, tumor which formed much more abundant reticulin.

The perithelial arrangement of the neoplastic cells in this tumor was due to intervascular necrosis. Such tumors in the brain, however, must begin as true peritheliomatous growths. The study of such cases as

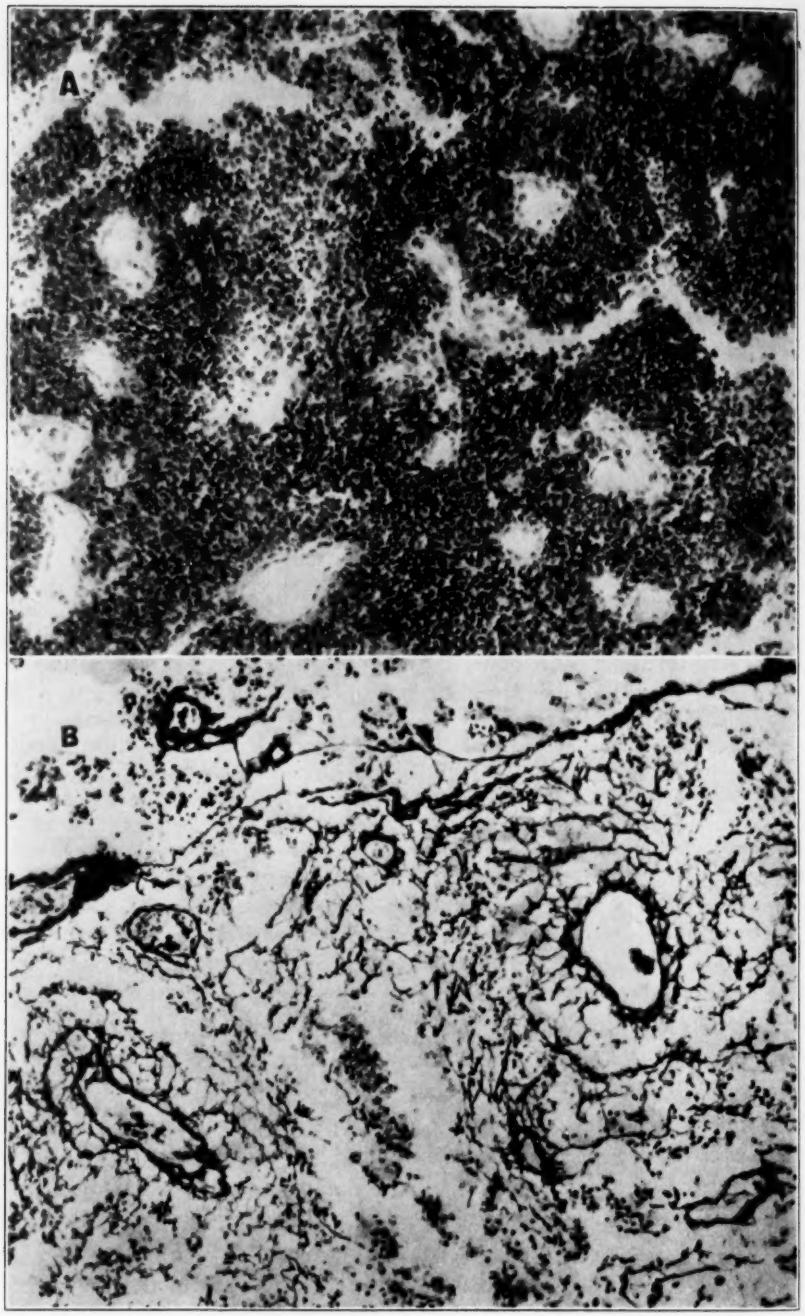

Fig. 4 (case 4).—*A*, hematoxylin and eosin; × 150. Intervascular necrosis of the tumor tissue. *B*, Perdrau's method; × 150. Reticulin fibrils in the preserved portion of the neoplasm radiating around the vessels.

those described by Eberth,[26] Jannsen,[27] Besold,[28] Cornil,[29] Wätzold,[30] Haeger,[31] Schaede,[32] Cassirer and Levy,[33] Connor and Cushing,[15] Manganotti,[34] Fried,[35] Mage and Scherer,[36] Greenfield,[14] Stevenson and Hyslop[37] and Környey[38] makes such an origin almost certain, even though the tumor is rarely found in the earliest stages of its growth. When later the neoplastic cells coalesce to form a solid mass, one can only suspect their origin from the perithelial leptomeningeal tissue.

Because of the extensive degeneration it was difficult to demonstrate in the present case the relationship of the reticulin to the blood vessels. In other cases (Bailey and Ley[39]) it has been clear that at first the reticulin lies around the vessels in concentric rings (fig. 5 *A* and *B*). When the rings are ruptured the reticulin radiates about the vessel as though it had exploded (figs. 6 *A* and *B*).

The presence of a ganglioneuroma in the medulla of the adrenal gland necessitates at least passing mention. The possibility that the intracranial tumor might be metastatic from this origin is negligible.

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36. Mage, J., and Scherer, H. J.: Tumeur cérébrale parvicellulaire se propageant dans l'espace de Virchow-Robin, J. belge de neurol. et de psychiat. **37**: 731, 1937.

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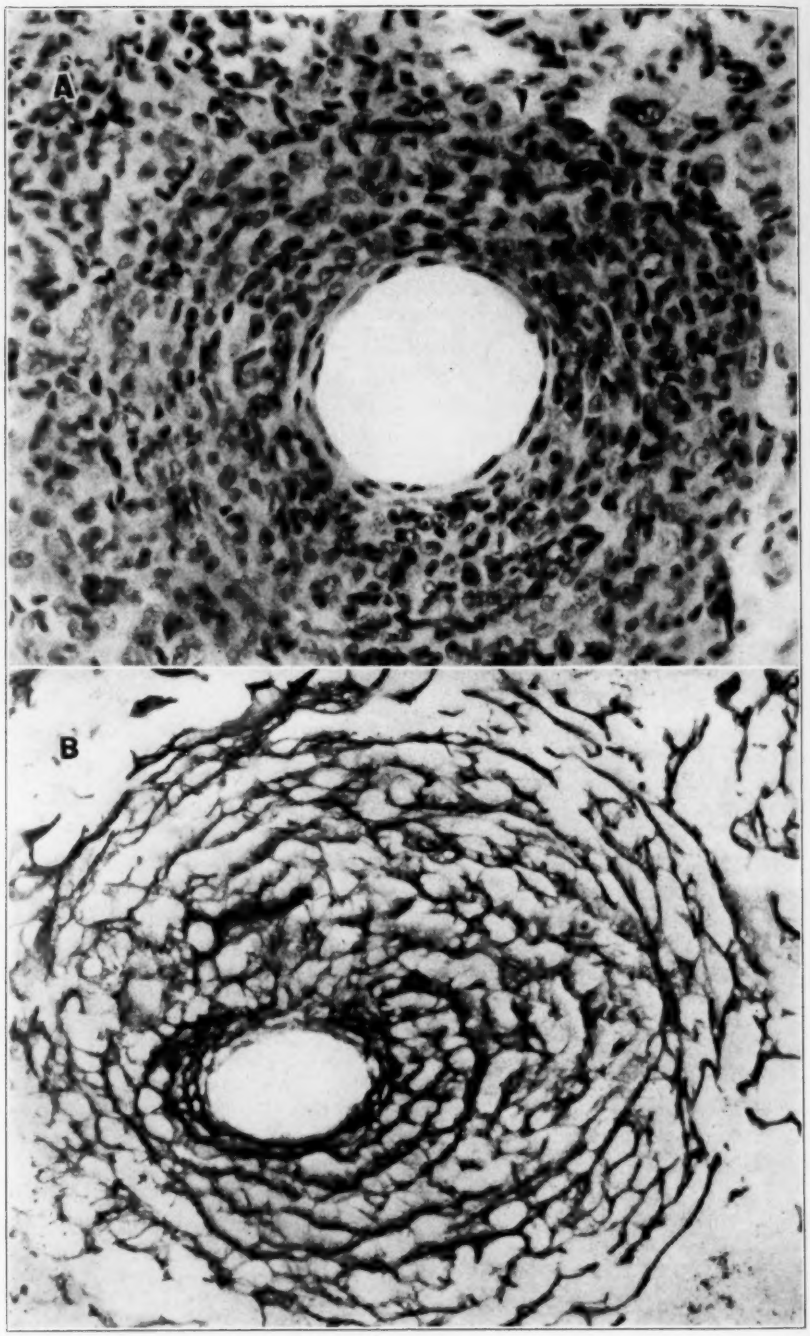

Fig. 5.—*A*, hematoxylin and eosin; × 300. Perithelial arrangement of the neoplastic cells in a sarcoma of the brain. *B*, Perdrau's method; × 300. Concentric arrangement of the reticulin fibrils, with the pia-glial membrane remaining intact, in the same tumor as that shown in figure 5 *A*.

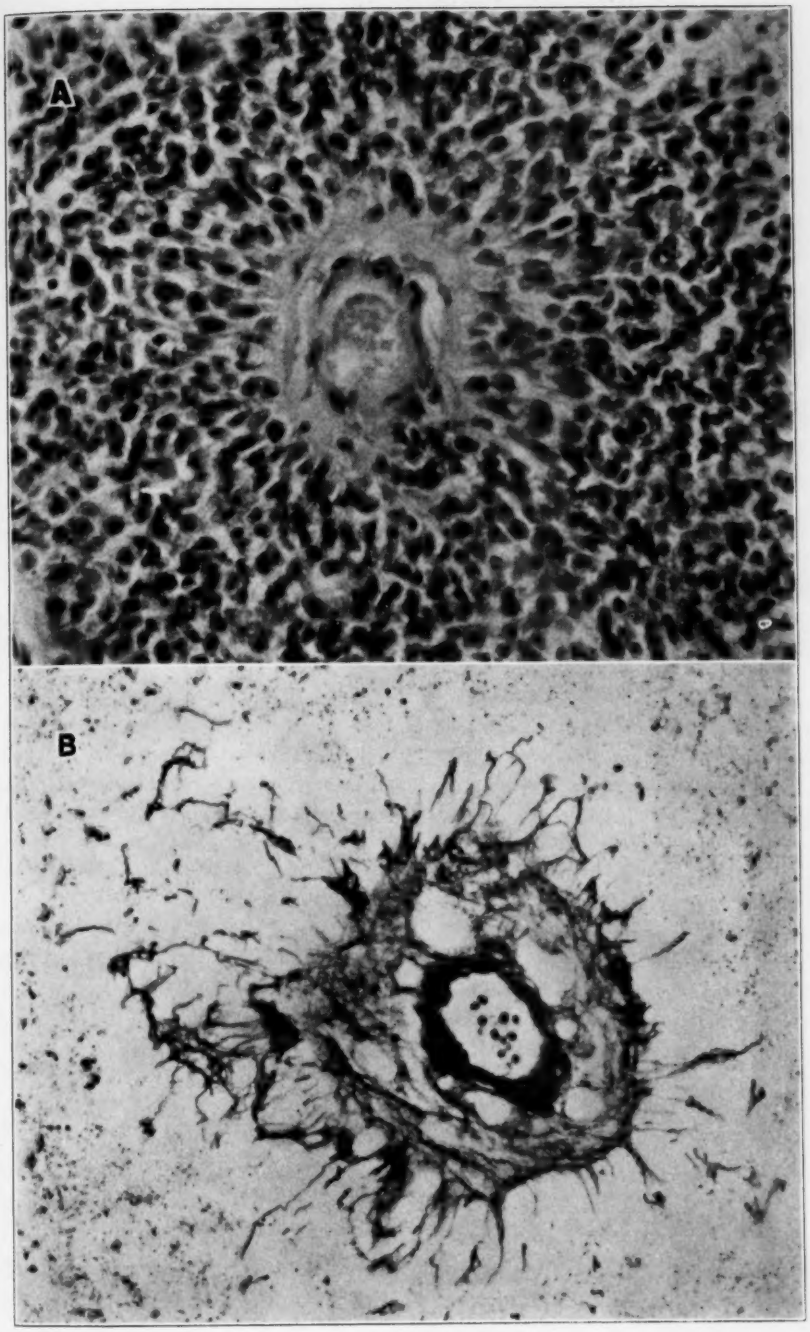

Fig. 6.—*A*, hematoxylin and eosin; × 300. Neoplastic cells radiating around a blood vessel in a sarcoma of the brain, the same tumor as that shown in figure 5 *A*. *B*, Perdrau's method; ×300. Picture similar to that in figure 5 *B*, with the reticulin fibrils radiating from the ruptured pia-glial membrane. From the same tumor as that shown in figures 5 *A* and *B* and 6 *A*.

Not only did the adrenal tumor appear entirely inactive but there were no metastases elsewhere and the structure of the intracranial tumor did not resemble in any way that of a malignant sympathicoblastoma.

PERIVASCULAR SARCOMA OF THE BRAIN OF A DOG

Finally, I shall mention briefly a sarcomatous tumor discovered accidentally in the brain of a dog by Dr. P. C. Bucy and Dr. E. M. K. Geiling in the course of experiments with diethylene glycol. The dog had previously been well, and, since the experiment was an acute one, the drug used cannot have been responsible for the origin of the tumor. Moreover, several such tumors have been shown me by Dr. Peter Olafson of the New York State Veterinary College, and it is hoped that he will report on them soon.

Microscopic Examination.—The center of the tumor was composed of a compact mass of cells with foci of necrosis, which were either fresh or replaced by thick strands of collagen. At the margin of the tumor the neoplastic cells were distinctly perivascular in distribution (fig. 7 *A*), while the surrounding nerve tissue appeared healthy. Some of the cuffs of cells broke through the pia-glial membrane and spread directly against the brain tissue. In the central portion of the tumor the cells were evidently proliferated to such an extent that the neural parenchyma had been destroyed completely, leaving a solid mass of tumor tissue. The cells were oval and had abundant cytoplasm. They resembled closely lymphocytes, plasma cells and large mononuclear cells. The last type of cells predominated. The nuclei of these cells were oval, lobulated or half-moon shaped, with crenated nuclear membrane. All were vesicular, and some had one or two nucleoli. The cytoplasm was eosinophilic, and vacuolation of the cytoplasm was frequently noticed. Mitotic figures were numerous. There was no capsule. Perdrau's method showed an irregularly distributed network of reticulin fibrils among the tumor cells, which were denser in the heavy cuffs of cells around the blood vessels (fig. 7 *B*).

The most striking feature in this case is the predominance of cells which resembled closely lymphocytes, plasma cells and mononuclear cells of the blood. These cells are of the nature of histiocytes and probably originated from those of the perithelium of the blood vessels. The reticulin fibers came probably from fibroblastic elements. In contrast to case 3, this case represents the other extreme of the microscopic picture of a sarcoma. In any sarcoma both histiocytes and fibroblasts may participate. Predominance of the one or of the other will influence the general microscopic appearance of the tissue and the degree of reticulum formation. The histologic picture in this case resembles that in Bailey's human case IX (fig. 63), reported in 1933.[39a]

Aring and Mayfield [40] have reported a case of meningioma occurring in a dog. The histologic picture of their tumor was different in many respects from that of this tumor.

39a. Bailey, P.: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

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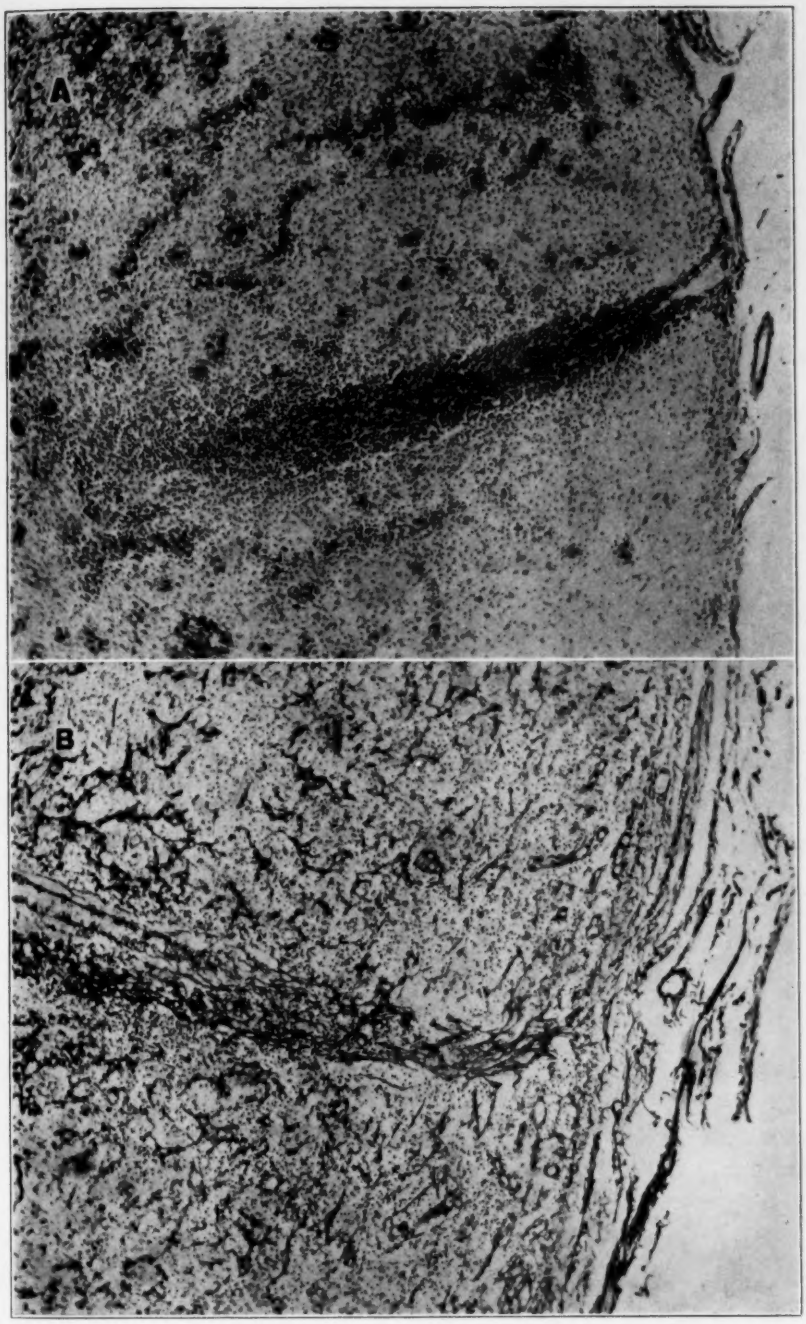


Fig. 7 (dog).—*A*, hematoxylin and eosin; × 60. Perithelial location of the neoplastic cells. *B*, Perdrau's method; × 60. Reticulin fibrils, more prominent around the vessels.

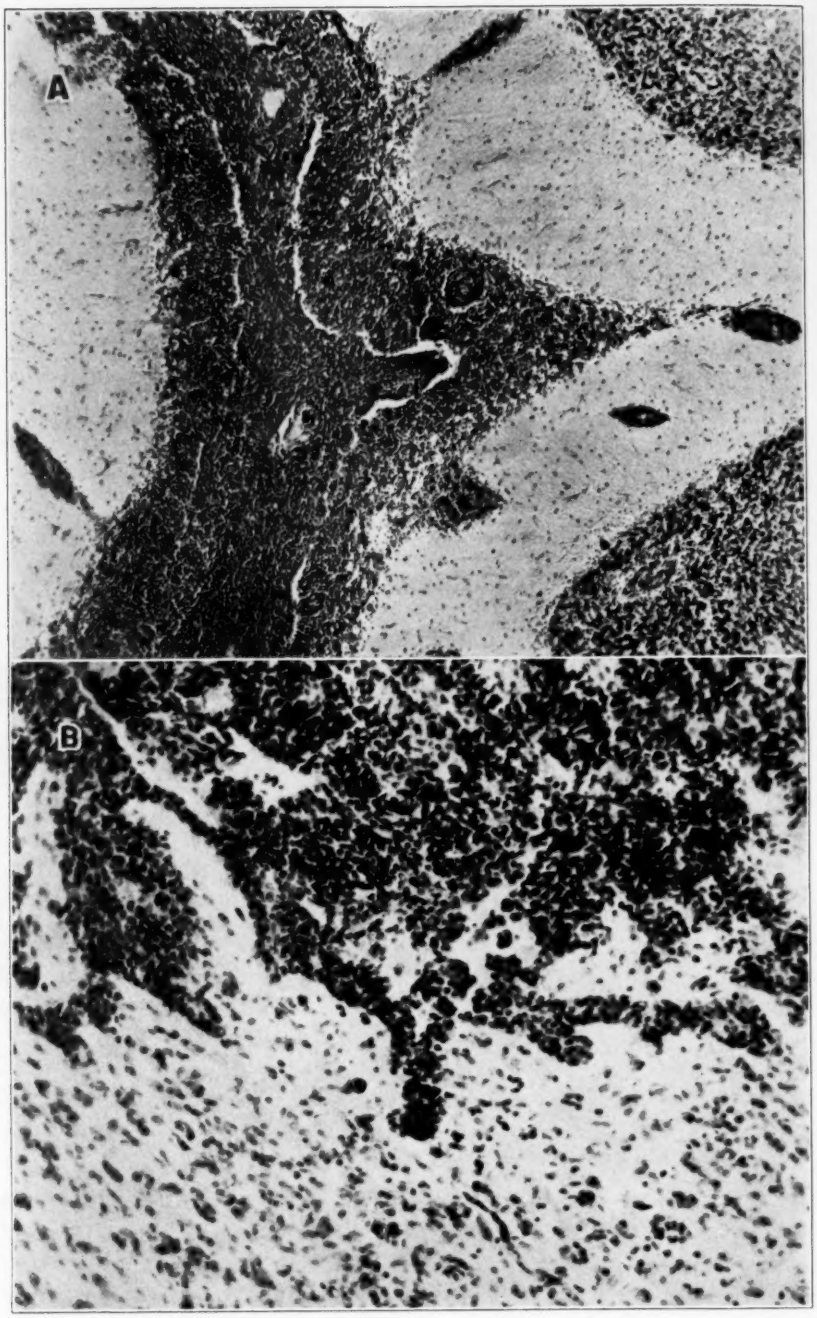


Fig. 8.—*A*, hematoxylin and eosin; × 60. Extension of the neoplastic process into the perivascular spaces of the molecular layer of the cerebellum. The tumor remains confined to the perivascular spaces. *B* (case 4), hematoxylin and eosin; × 150. Direct advance of the neoplastic cells against the brain tissue. No formation of capsule.

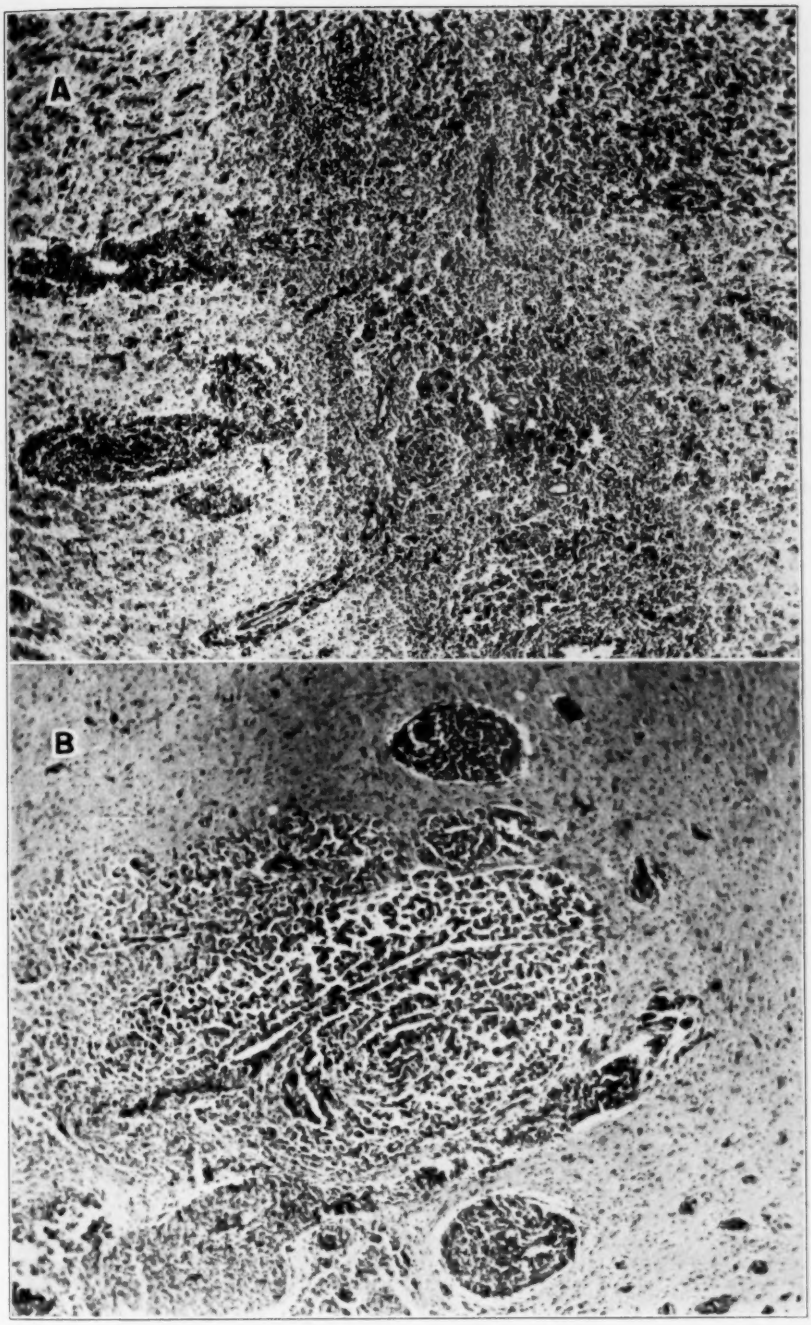


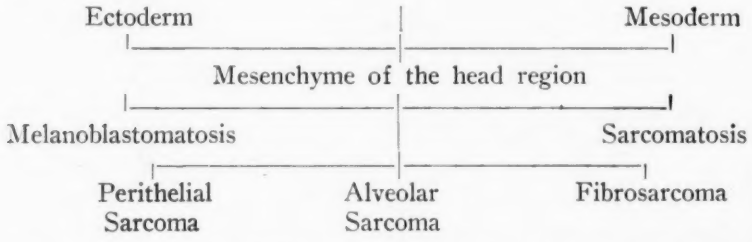
Fig. 9.—*A*, hematoxylin and eosin; × 45. Spread of a meningeal sarcoma into the surrounding cerebral tissue: on the left, by way of the perivascular spaces and, on the right, diffusely into the neural parenchyma. *B*, hematoxylin and eosin; × 60. Spread of a meningeal sarcoma. Around two vessels the cells are confined to the perivascular spaces, while between them the tumor has broken out and invades the neural parenchyma diffusely.

CONCLUSIONS

The tumors described have certain features in common. They are of connective tissue nature and must be derived from the leptomeningeal tissue. They are very cellular and contain numerous mitoses. They form scanty intercellular substances characteristic of connective tissue. They spread mainly along the perivascular and leptomeningeal spaces, but may break out of them into the neural parenchyma and then spread diffusely, without forming a capsule.

Their differences may be variously accounted for. Those which gain access to the subarachnoid spaces have an easy pathway for spreading. Metastatic sarcoma spreads in the leptomeningeal spaces in the same manner. But there are reasons to believe that some of these diffuse tumors may originate simultaneously in many parts of the leptomeningeal tissue. The more rapidly growing cells, as elsewhere, form less intercellular fibrillary material. Also, the type of the cell must have some influence in determining the amount of intercellular fibrillary material. Those cells which differentiate in the direction of meningothelial cells do not form reticulin. Those which differentiate toward fibroblasts form reticulin. The state of health of the neoplastic cells also plays a role, as may be seen in case 4, in which reticulin was formed only among the healthy cells near the blood vessels. I have already noted how in this tumor intervascular necrosis arises from faulty nutrition of the neoplastic cells. All of these factors interplay to bring about the final microscopic picture. The neoplastic tissue of these tumors is a living, growing structure, which, under the influence of many factors in varying proportions, gives rise to the infinitude of microscopic appearances, from which I have ventured to isolate the preceding types. It should be remembered, however, that no two of these tumors are ever exactly alike.

The relationships of these tumors may possibly be expressed by the following diagram:



The use of the Perdrau or a similar method for the impregnation of reticulin is essential for the recognition of these tumors.

No clinical syndrome characteristic of these intracranial sarcomatous tumors can be recognized.

EFFECTS OF INTRAVENOUS INJECTION OF INSULIN IN TREATMENT OF MENTAL DISEASE

PRELIMINARY REPORT OF CLINICAL OBSERVATIONS

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NEW YORK

Recently the value of prolonged hypoglycemic coma in the treatment of schizophrenia has been emphasized.[1] One of us (P. P.) and several co-workers [2] have called attention to the frequent occurrence of vertebral fractures as a result of convulsions in the course of such treatment. The present investigation was undertaken to determine whether hypoglycemic shock itself, without prolonged coma, might be of benefit in the treatment of patients with mental disease.

The aim was to produce hypoglycemic symptoms as rapidly as possible and to observe whether the patient's behavior was altered. For this reason insulin was administered intravenously.

Since Lyman, Nicholls and McCann,[3] in 1923, investigated the effects of intravenous administration of insulin on normal and diabetic subjects, there have been many experiments with the intravenous use of insulin, both in man and in various animals. Although most of these investigations have been concerned with the establishment of blood sugar curves,[4] there have been isolated studies of tolerance to repeated injec-

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4. (*a*) Thaysen, T. E. H.: Clinical Investigation into the Effect of Intravenous Injection; Insulin: Blood Sugar Curve in Diabetes, Acta med. Scandinav. **73**: 408-424, 1930. (*b*) Nordsted, A.; Norgaard, A., and Thaysen, T. E. H.: Clinical Investigations into Effects of Intravenous Injections: Hypoglycemic Symptoms in

(Footnote continued on next page)

tions in dogs,[5] and also of the effects of this method of administration of insulin on endocrine states,[6] on the blood pressure and the blood picture [4c] and on the blood sugar curves in diseases involving disturbances of carbohydrate metabolism.[7] As far as we have been able to determine, however, there has been no previous report of the effects of repeated injections of large doses of insulin intravenously in the treatment of mental disorder.

PROCEDURE

Patients treated with intravenous administration of insulin first received over a period of several days small doses of insulin hypodermically to determine whether there was any unusual sensitivity. Then, daily before breakfast at about 8 a. m., each patient received an injection of 12 units into a cubital vein. The injections were given as rapidly as possible. The patients were then permitted to remain in bed for from one to two hours. Ordinarily the period of hypoglycemia was terminated with a routine breakfast, but if patients had manifested marked symptoms they received 50 cc. of Karo syrup or about 200 cc. of a 25 per cent solution of dextrose in water flavored with lemon. Only on rare occasions was it necessary

TABLE 1.—*Distribution of Cases According to Diagnosis*

Diagnosis	Number of Cases
Schizophrenia	15
Anxiety hysteria	2
Obsessive-compulsive neurosis	2
Paranoid psychosis	1
Depressive psychosis	3
Total	23

to administer 20 cc. of a 50 per cent solution of dextrose intravenously. A warm shower usually followed the termination of the hypoglycemic state. Six morning treatments were given each week.

The initial dose of 12 units was increased by 5 unit increments as more marked effects were desired. The largest amount injected at one time was 90 units. A nurse was constantly in attendance, and a physician was always available during the period of treatment.

EFFECTS OF INSULIN INJECTED INTRAVENOUSLY

Twenty-three patients, 8 males and 15 females, were treated over a period ranging from two to thirteen weeks. The clinical diagnoses in these cases are given in table 1. Some of the patients had previously been treated with insulin

Normal Individuals, ibid. **73**:125-138, 1930. (*c*) Kugelmann, B.: Ueber die Beziehungen zwischen Insulin und Adrenalen in menschlichen Organismus, Klin. Wchnschr. **10**:59-62 (Jan. 10) 1931.

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coma (Sakel technic), with metrazol convulsions or with both. The significant data pertaining to the individual cases are recorded in table 2.

The symptoms produced during the hypoglycemic state resulting from the intravenous injection of insulin were essentially similar to those seen after hypodermic injection. The phenomena of hypoglycemic shock as previously reported [1] were also noted in our study, i. e., symptoms of involvement of the pyramidal tracts, myoclonic movements, rhythmic movements, sensory disorders, aphasic disturbances and vegetative symptoms, such as excessive perspiration, vasomotor alterations and cardiac arrythmias. There were, however, several significant differences. With intravenous administration of insulin the shock symptoms developed much more rapidly, and patients receiving doses adequate to produce definite clinical symptoms were usually asleep within forty-five minutes. With sufficiently large doses stupor or coma might appear within the same interval. Spontaneous recovery from all these states was the general rule. Many patients complained shortly after injection of "yellow spots in front of the eyes." Nausea and abdominal pain were frequent complaints. In 4 cases allergic phenomena were noted. These were both general and local. Two patients (cases 19 and 23, table 2) on the twenty-sixth day of treatment showed warm, red, itching, elevated, irregularly outlined areas, about 3 cm. in diameter, over the site of injection. These disappeared completely within twenty-four hours. Another patient (case 13, table 2), about five minutes after the injection of 17 units on the twenty-eighth day of treatment, suddenly experienced generalized severe itching of the entire body and of the eyes in particular. These symptoms subsided in about half an hour. This reaction, together with typical allergic wheals, reappeared from time to time in this patient.

An increase in emotional instability was also observed. Weeping was in some instances almost convulsive, and after it subsided in about fifteen minutes, was followed by a feeling of relief and relaxation. Anxiety as a symptom appeared to diminish during the period of treatment. In general it was evident that the emotional responsiveness of the patients was enhanced, and they were frequently made more amenable to psychotherapy and to nursing care.

Transitory alterations in the mental status of the patients were outstanding during the period of treatment and in some instances continued for a few hours thereafter. Agitated and excited patients were quieted; states of confusion cleared, and dulness and apathy gave way to increased alertness. In some cases beneficial changes gradually persisted over longer intervals following the period of treatment until definite improvement in clinical behavior was maintained.

The patients in our series revealed the same marked variations in sensitivity as have been observed under treatment with hypodermic injections of insulin. Some showed pronounced clinical symptoms after the rapid injection of only 12 units intravenously, while 2 patients manifested comparatively few symptoms when 90 units was injected. With small doses tolerance was usually established, and in this state of tolerance raising or lowering the dose increased the severity of the hypoglycemic reaction. In general, it was possible to reach a higher dose at which reactions of fairly constant severity could be obtained daily.

It has been noted that in some persons insulin has a biphasic effect or a delayed reaction; i. e., a period of hypoglycemia will, after a period of recovery, be followed by another interval of hypoglycemia. These biphasic effects were also seen repeatedly after the injection of insulin intravenously. One patient, about one and a half hours after injection, was alert and drank dextrose, only to slip back within five minutes or so into a state of coma deeper than the primary reaction. About thirty minutes later she again recovered spontaneously.

TABLE 2.—*Evaluation of Results of Intravenous Method of Insulin Therapy*

No.	Patient	Age, Yr.	Diagnosis	Duration of Illness	Previous Treatment	Number of Intravenous Treatments	Duration of Intravenous Treatment, Wk.	Total Number of Insulin Units Given Intravenously	Maximum Insulin Units in Intravenous Dose	Degree of Improvement
20	E. R.	26	Schizophrenia (hebephrenic)	3 mo.	.....	47	8	1,031	50	Recovery
23	A. W.	35	Schizophrenia (hebephrenic)	8 yr.	.....	59	10	1,374	50	Marked
21	C. S.	32	Schizophrenia (hebephrenic)	3 mo.	Insulin shock	69	11½	1,772	70	Marked
19	A. R.	13	Schizophrenia (catatonic)	2 yr.	.....	66	11	1,559	50	Slight
18	J. Q.	35	Schizophrenia (catatonic)	2½ yr.	Insulin shock and metrazol	72	12	3,790	90	None
17	M. P.	35	Schizophernia (hebephrenic)	7 mo.	.....	62	10½	2,074	60	None
15	T. M.	22	Schizophrenia	1 yr.	.....	50	8½	1,400	50	Slight
11	E. G.	25	Schizophrenia (hebephrenic)	2 yr.	.....	64	11	1,606	50	Slight
10	D. M.	18	Schizophrenia (hebephrenic)	2 yr.	Metrazol	10	2	120	15	None
9	L. C.	42	Schizophrenia (paranoid)	5 yr.	.....	58	10	1,117	30	Marked
8	S. T.	18	Schizophrenia (simple)	2 yr.	.....	29	5	564	50	Marked
6	S. M.	22	Schizophrenia (simple)	Over 3 yr.	Metrazol	40	7	1,875	50	None
5	A. H.	30	Schizophrenia (simple)	5 yr.	.....	70	12	1,876	55	None
3	L. C.	19	Schizophrenia (hebephrenic)	3 mo.	.....	35	6	468	30	None
1	W. B.	24	Schizophrenia (mixed)	Over 2 yr.	.....	27	4½	379	25	None
12	D. L.	39	Depressive psychosis	4 mo.	Metrozol	44	8	1,960	55	Marked
13	E. L.	39	Depressive psychosis	2 yr.	.....	76	13	3,918	85	None
14	E. M.	37	Depressive psychosis	7 mo.	.....	78	13	1,833	45	Slight
16	A. M.	29	Anxiety hysteria	2 yr.	.....	53	9	1,245	40	None
2	E. B.	30	Anxiety hysteria	Over 8 yr.	Metrazol	55	9½	1,604	50	Slight
7	L. S.	20	Obsessive compulsive neurosis	3 yr.	Metrazol	32	5½	656	40	None
22	L. W.	20	Obsessive compulsive neurosis	5 yr.	Metrazol	46	8	1,542	70	None
4	M. C.	41	Paranoid psychosis	5 mo.	.....	38	6½	664	45	None

In all, 23 patients with a variety of psychiatric disorders were treated over a period of from two to thirteen weeks. One patient recovered. Ten others showed some improvement in their clinical status. Of the 10 patients with schizophrenia treated over a period of eight weeks or more, 1 recovered, 3 were much improved, 3 were slightly improved and 3 remained unimproved. Those considered much improved were able, despite residual symptoms, to adjust socially at a level paralleling their prepsychotic behavior. Those in the category of slight improvement showed a definitely increased ability to adjust to the hospital routine, but did not reach their prepsychotic level of behavior because of residual symptoms.

It is noteworthy that even the patients of all diagnostic groups whose mental state was not improved manifested improvement in appetite, which reduced feeding problems. A sedative effect was also obtained which enabled patients to sleep better at night, and at times a stimulating effect from the treatment produced a feeling of increased energy and well-being for several hours. The nursing problems in many cases were simplified. The 15 patients treated for more than eight weeks had an average gain in weight of 7.3 pounds (3.3 Kg.), with the range of increase varying from 0 to 17 pounds (7.7 Kg.).

No convulsions resulted from this treatment, nor were there any observable injuries.

COMMENT

There is considerable difference of opinion regarding the beneficial effects of insulin hypoglycemia in the treatment of mental diseases, and of schizophrenia in particular. Our studies were primarily directed to determine whether the hypoglycemic shock itself, produced as rapidly as possible and with a minimum of coma, was of benefit in the treatment of patients with mental disease. It was found that insulin administered intravenously produced symptoms of hypoglycemic shock comparatively rapidly, and that these repeated daily shocks were of benefit. Forty-eight per cent of our patients treated two weeks or longer showed definite improvement, as previously defined. In general there was improvement in the physical condition of the patient.

This method of treatment had numerous advantages over the usual hypoglycemic shock technic. It was completed within two hours. Patients usually recovered spontaneously from the shock to drink the dextrose solution offered them, and none of the patients had convulsions or received any detectable injury. The total amount of insulin per patient was less than that given during the usual hypodermic insulin therapy. A minimum of nursing supervision was necessary.

There was considerable variation in the effects of different doses of insulin on the patients. Several manifested rapid improvement with the injection of 12 units intravenously. In the schizophrenic group 3 patients showed by the end of the first week of treatment increased alertness and responsiveness to the environment, a more labile affect and a striking improvement in ability to carry out the routine. Later,

however, larger doses were necessary to obtain similar effects. Other patients did poorly on the small doses and showed no signs of improvement. With larger doses, however, some of these improved. Several patients were not benefited by comparatively large doses and temporarily complained that their thoughts came more slowly and that they were much more fearful. Increased anxiety with larger doses was particularly true of the psychoneurotic patients.

We were at times impressed with the transitory improvements which occurred during the treatment. It appeared likely that there might be a large group of patients with schizophrenia who would derive considerable benefit from the therapeutic method here described. However, it was also evident that while the intravenous method of shock therapy itself was beneficial, there might be a group of patients for whom the prolonged coma produced by Sakel's method was more desirable. Eventually it may be possible to formulate indications for the intravenous induction of shock, on the one hand, or for prolonged coma, on the other. A much larger series of cases and several years of further investigation are essential before any conclusive statements can be made.

It is encouraging that 70 per cent of the patients with schizophrenia who were treated over a period of more than eight weeks revealed some improvement in mental status at a time when the dose of insulin desired and the indications for treatment were little understood. There was evidence that such treatment of the depressive psychoses might be beneficial. Less favorable observations were made during the treatment of patients with psychoneuroses.

The mechanism whereby the improvement resulted remains obscure. It was evident that the favorable effects most generally obtained were those in the sphere of the vegetative nervous system. As a group the patients ate better, slept better and showed definite affective changes. The psychotic trends were less markedly influenced. It seemed that the effects were primarily the results of altered function of the vegetative nervous system, while other cerebral functions were influenced to a lesser degree. Gellhorn [8] has emphasized the role of stimulation of the sympathetic nervous system in the mechanism producing improvement in schizophrenia by the usual hypodermic method of insulin therapy.

The allergic phenomena here reported were both local and general. They may have been the result of impurities in the insulin used. Investigation of these phenomena are being made, and further studies are to be carried on with a solution of zinc insulin crystals.

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8. Gellhorn, E.: Effects of Hypoglycemia and Anoxia on the Central Nervous System, Arch. Neurol. & Psychiat. **40**:125-145 (July) 1938.

SUMMARY AND CONCLUSIONS

Twenty-three patients, 19 of whom had psychoses and 4 psychoneuroses, were treated mornings with intravenous injections of insulin over a period of from two to thirteen weeks to produce rapid hypoglycemic shock with a minimum of coma. The dosage varied from 12 to 90 units, and the injections were administered as rapidly as possible. Marked hypoglycemic symptoms, at times with coma, were produced within forty-five minutes, and spontaneous recovery was general within two hours. Occasionally a biphasic effect was observed. Allergic symptoms appeared in 4 patients.

The dose of insulin was increased until rapidly developing hypoglycemic shock was induced. With this treatment there was general improvement in the physical condition of the patients, and 48 per cent of all those treated revealed some degree of mental improvement. Ten patients with schizophrenia were treated over a period of two months or more, and 70 per cent showed some improvement in their mental state. None of the patients had convulsions, nor were there any detectable injuries during the course of treatment. The utilization of this method in the treatment of mental disease deserves further investigation.

SERUM PROTEIN, NONPROTEIN NITROGEN AND LIPOIDS IN SCHIZOPHRENIC AND MANIC-DEPRESSIVE PSYCHOSES

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This report is concerned with the variations which occur in the protein and lipoid contents of the blood serum of schizophrenic and manic-depressive patients during exacerbations and remissions of symptoms. The values have been compared with those obtained in similar long term studies on persons in good health. In addition, the general levels of lipoids in the two groups of psychotic patients and in the control group have been compared.

Previous reviews of biochemical studies of dementia praecox and manic-depressive psychosis, such as those of Page [1] and, more recently, of McFarland and Goldstein,[2] have revealed marked differences in the results obtained by various observers. The sources of this confusion can be summarized as follows: The large group of patients with so-called schizophrenia exhibit a variety of conditions that are very different and may not be related. Furthermore, the condition of each patient varies enormously in the course of the disease. Differences in methods, lack of control studies and errors in methods undoubtedly play a part in producing differences in results. An insufficient number of determinations is also common.

Recently these sources of error have come to be recognized and avoided. For example, well controlled metabolic studies on schizophrenic

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Some of the material in this paper is derived from the thesis of Dr. Robert W. Biach which was presented in partial fulfilment of the requirements for the degree of Doctor of Medicine from the Yale University School of Medicine, June 1938.

1. Page, I. H.: Chemistry of the Brain, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

2. McFarland, R. A., and Goldstein, H.: The Biology of Dementia Praecox, Am. J. Psychiat. **95**:509, 1938.

persons have been conducted at the Worcester State Hospital.[3] The group of investigators here has reported that recent analysis of their long term and extensive metabolic studies "revealed that in practically 80% of the variables, the intra-individual variation of the schizophrenic individual was greater than that of the normal control." [4]

Since 1925, Gjessing [5] has been conducting a carefully controlled long term study of schizophrenic subjects. He has found that patients subject to periodic attacks of catatonic stupor suffer marked fluctuations in nitrogen metabolism (as measured by balance studies) during changes in mental status. The unique and valuable feature of this study lies in the fact that these patients have lived, during the years of observation, on a standard diet, no variation being allowed in the amount or quality of food. Gjessing's studies suggest that marked fluctuations might well be found in the proteins and the albumin and globulin fractions, and possibly in the nonprotein nitrogen, of the blood during the acute and changing phases of catatonic schizophrenia. Furthermore, the frequency with which suggestive evidences of hepatic dysfunction have been described would lead one to expect to find disturbances in the relation between albumin and globulin in some phase of schizophrenia. For these reasons, the nonprotein nitrogen, the total proteins and the albumin and globulin fractions of the blood serum have been studied.

A preliminary study of the fatty acids of the serum in patients with manic-depressive psychosis, begun by us a number of years ago, showed that these substances tend to rise during the severe phases of the manic or the depressive condition and that they fall with recovery. In the course of this work it was found that many complicating factors may obscure this trend in the lipoids. Subsequently, a detailed investigation of the conditions which control the level of serum lipoids was undertaken. The relevant results of these complementary studies will be considered later in the discussion of methods. The following observations, however, will be made here for the sake of emphasis.

It has been found that many of the patients, regardless of the primary disease, who manifested extreme disorders of the vegetative nervous system, and also not infrequently muscle tremors, disturbances of facial expression and associated movements and other evidences of disorder of the brain stem, had values for the fatty acids and cholesterol of the serum that were considerably above the high limits of normal. Instances in which a disorder of the brain stem was associated with a high lipoid content were found among patients with tumors in the region of the

3. Hoskins, R. G., and Jellinek, E. M.: The Schizophrenic Personality with Special Regard to Physiologic and Organic Concomitants: The Biology of the Individual, A. Research Nerv. & Ment. Dis., Proc. **14**:211, 1934.

4. McFarland and Goldstein,[2] p. 543.

5. Gjessing, R.: Disturbances of Somatic Function in Catatonia with Periodic Course and Their Compensation, J. Ment. Sc. **84**:608, 1938.

third ventricle, postencephalitic syndromes, thalamic syndromes of unknown origin and diabetes mellitus. Disturbances in mood may also be associated with these disorders of the brain stem. In view of these findings,[6] the lipoid studies were extended to patients with schizophrenia, particularly those with catatonic syndromes, who commonly also have severe and general disturbances of the vegetative nervous system.

MATERIAL

The clinical material falls into two main divisions, according to the number of blood studies. Group 1, representing long term studies, includes the patients on whom measurements of the lipoid and protein contents of the serum were made repeatedly (four to eighteen determinations) during periods ranging from one month to three years. In general, the observations were made when the patient's condition changed. Group 2, representing extensive studies, includes patients on whom measurements of the lipoids and proteins were made on only one or two occasions. Group 1 includes 14 patients with schizophrenia, 11 with manic-depressive psychoses and 7 with psychoses presenting both schizophrenic and manic-depressive features. It should be noted that all but 1 of these patients were experiencing rapidly changing and severe symptoms. Group 2 includes 34 patients with schizophrenia and 62 with manic-depressive psychosis. Control studies for group 1 were made on 10 persons in good health for periods ranging from three months to three years. The control studies for group 2 were derived from observations on 73 men and women in good health. Most of the results of these control observations may be found in articles published in 1936[7] and 1937.[8]

An additional investigation of the normal variations in nonprotein nitrogen, total proteins and albumin and globulin was made during the past year.

CLINICAL METHODS

All of the patients were under observation in the psychiatric clinic of the New Haven Hospital and were carefully and completely investigated according to the present day conventional psychiatric and medical methods. The diagnoses were made by members of the senior staff independently of us. When the usual impassé was reached in the case of patients presenting symptoms of both schizophrenic and manic-depressive conditions, we classified them as presenting an intermediate syndrome.

Previous studies in this hospital have shown that many common disturbances in patients may be associated with low or high levels of the lipoids and proteins in the blood. Particularly relevant to the present study are the following observations: (1) Severe malnutrition which lowers the serum proteins and lipoids is frequently present;[9] (2) closely related to nutrition is fluid intake, which if

6. Gildea, E. F., and Man, E. B.: Lipemia in Patients with Pituitary Disease Contrasted with That of Patients with Disorders of the Brain Stem, A. Research Nerv. & Ment. Dis., Proc. (1939), to be published.

7. Gildea, E. F.; Kahn, E., and Man, E. B.: The Relationship Between Body Build and Serum Lipoids and a Discussion of These Qualities as Pyknophilic and Leptophilic Factors in the Structure of the Personality, Am. J. Psychiat. **92**:1247, 1936.

8. Man, E. B., and Gildea, E. F.: Variations in Lipemia of Normal Subjects, J. Biol. Chem. **119**:769, 1937.

9. Man, E. B., and Gildea, E. F.: Serum Lipoids in Malnutrition, J. Clin. Investigation **15**:203, 1936.

inadequate results in hemoconcentration and an apparent rise in the lipoids and proteins of the serum.[10] As changes in weight are common in these mental disorders, the weights of the patients were recorded. Unless otherwise indicated, the patients were given optimal diets, including 2 to 3 liters of fluid daily, and tube feedings were resorted to if necessary. When dehydration had been present, this was noted in the tables. In the present study dehydration refers to the clinical signs of dryness of the tongue and skin. Underactivity of the thyroid increases the lipoids, and overactivity reduces them. In general, it is probable that function of the thyroid was normal in the patients studied, but, as will be described later, it was difficult to be certain in cases of some of the severely psychotic patients. Disorders in function of the liver and kidneys may affect lipoid metabolism. Demonstration of normal function in the kidney was a relatively simple problem, but proved difficult in the case of the liver. The latter problem will be taken up in the discussion of results.

Because of the observations on the relation of disorders of the brain stem to a high lipoid content of the serum, particular attention was devoted to the presence and severity of vasomotor instability, tremor, masklike facial expression and other features suggestive of involvement of the brain stem. Like workers in other institutions, we found extreme difficulty in making any quantitative estimate of the degree of vasomotor instability, disturbance in mood or tremor. For this reason only marked qualitative differences have been recorded.

METHODS

All samples of blood were taken from an arm vein when the patient was in the postabsorptive state. Serum from these samples was analyzed in duplicate for total fatty acids, cholesterol, total protein, albumin and globulin by methods previously described.[11] It should be noted that the titrated fatty acids are now considered to contain all of the phosphatide fatty acids. Nonprotein nitrogen was determined on the trichloroacetic acid filtrate of whole blood by a micro-Kjeldahl technic. The errors involved in the chemical determinations, except those of albumin and globulin, were negligible as compared with the normal daily variations.[8] In the 100 consecutive duplicate determinations of serum cholesterol, it was found that the correlation between one duplicate and the other was 0.978, or that one could be estimated from the other within a probable error of ± 10.84 mg. per hundred cubic centimeters of serum. The correlation between duplicate determinations of fatty acids was 0.987, and the probable error of estimate, ± 0.49 milliequivalents.

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10. (*a*) Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: Plasma Proteins in Relation to Blood Hydration: IV. Malnutrition and the Serum Proteins, J. Clin. Investigation **8**:577, 1930. (*b*) Man, E. B., and Peters, J. P.: Permeability of Capillaries to Plasma Lipoids, ibid. **12**:1031, 1933.

11. (*a*) Man, E. B., and Gildea, E. F.: A Modification of the Stoddard and Drury Titrimetric Method for the Determination of the Fatty Acids in Blood Serum, J. Biol. Chem. **99**:43, 1932; (*b*) Notes on the Extraction and Saponification of Lipids from Blood and Blood Serum, ibid. **122**:77, 1937. (*c*) Man, E. B., and Peters, J. P.: Gravimetric Determination of Serum Cholesterol Adapted to the Man and Gildea Fatty Acid Method with a Note on the Estimation of Lipoid Phosphorus, ibid. **101**:685, 1933. (*d*) Man, E. B.: A Note on the Stability and Quantitative Determination of Phosphatides, ibid. **117**:183, 1937. (*e*) Bogdanovitch, S. B., and Man, E. B.: The Effects of Castration, Theelin, Testosterone and Antuitrin-S on the Lipoids of Blood, Liver and Muscle of Guinea Pigs, Am. J. Physiol. **122**:73, 1938. Bruckman, D'Esopo and Peters.[10a]

Sperry, Page and Boyd and their associates and we [8] have found that the lipoid content of the serum of a normal person in the postabsorptive state is subject to rather large variations. The question of the amount of these variations is rendered almost pointless if data obtained by the colorimetric or the nephelometric method are used, because, as has been repeatedly shown, these methods are often subject to error amounting to more than 25 per cent.[11c] On this account, only the data obtained by the digitonin methods for cholesterol and the titrimetric and oxidative technics for fatty acids were considered.

Our studies on 10 persons in good health showed a considerable intrapersonal difference in the amount of variation in the lipoids. In 1 person studied either at fortnightly or at monthly intervals for three years the maximum and minimum values for cholesterol varied by as much as 31 per cent, those for the fatty acids by 37 per cent and those for proteins by 14 per cent. These results are in agreement with those of Sperry. It should be considered, however, that the values for only 1 person varied to this extent and that those for the rest of the subjects varied much less. While this method of taking the most extreme change found in normal persons as the beginning of pathologic variation represents an oversimplification of the statistical problem, it also clarifies the problem of relating the data to complex clinical variables.

In interpretation of the studies on patients, changes in cholesterol of more than 55 mg. per hundred cubic centimeters, in fatty acids of 3.2 milliequivalents, in total proteins of 1 per cent, in albumin of 1 per cent, in globulin of 1 per cent and in nonprotein nitrogen of 9 mg. per hundred cubic centimeters have been considered beyond the normal limits.

DATA

In presenting the data it has been necessary, owing to limitations of space, to utilize tables which give a bare summary of the relevant observations. Charts of representative patients have been employed to illustrate further details of the changes observed. In tables 1, 2 and 3 are summarized the results of the studies on the three groups of patients: 14 with schizophrenia, 11 with manic-depressive psychosis and 7 with intermediate psychoses. The minimum values for the nonprotein nitrogen of the blood and for the total proteins, the albumin and globulin fractions, the fatty acids and the cholesterol of the serum are given, in addition to the differences between these values and the maximums reached by each constituent. Changes in weight of less than 10 pounds (4.5 Kg.) have been found in this department to have no effect on serum lipoids. Consequently, such minor changes have been indicated by 0, while those above 10 pounds have been recorded.

The degrees of change in clinical status have been recorded as follows: Recovery from a severely psychotic state to a point at which the patient could get along well at home has been indicated by $+++$. Change from the status requiring feeding with a spoon or tube, special treatment with packs and continuous tub baths to one of social adjustment to ward routine, but not of recovery sufficient for discharge from the hospital, has been rated as $++$. Lesser fluctuations in the condition have been rated as $+$, and a slow downhill course as $-$. The clinical condition has been indicated by the following abbreviations: "Ma." denotes the classic noisy, overactive, euphoric and occasionally irritable manic state; "MaD.," a manic period followed by a depressed state during the period of study; "D.," depressed mood and little energy; "A.D.," restlessness and anxiety, combined with depressed mood and complaints of lack of energy and interest; "Cat.," catatonic stupor during a part of the observation period; "Cat.E.," stereotyped state of excitement and overactivity, and "S.," schizophrenia of the slowly progressive sort, with some hebephrenic features. In the case of the patients who at various times presented symptoms suggestive of a manic-depressive con-

TABLE 1.—*Variations in Serum Proteins, Nonprotein Nitrogen and Lipoids in Schizophrenic Patients*

Patient No.	Sex	Age, Yr.	Duration of Illness, Mo.	Clinical Condition	Change in Weight, Lb.	Change in Mental Status	Blood Nonprotein Nitrogen, Mg. per 100 Cc.		Serum									
									Protein, Percentage		Albumin, Percentage		Globulin, Percentage		Fatty Acids, mEq.		Cholesterol, Mg. per 100 Cc.	
							Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference
1742	M	18	24	Cat.	0	+	25	6	6.0	1.9	4.6	1.5	1.5	0.5	8.3	1.6	121	38
1449	F	24	36	Cat.	0	++	19	20	6.1	1.4	3.8	1.3	1.6	1.2	8.9	2.8	163	45
1587	M	33	12	S.	0	+	22	3	6.2	0.3	4.3	0.3	1.7	0.2	7.8	0.4	120	11
1722	M	41	108	S.	0	−	25	14	6.0	1.2	3.8	0.5	2.9	0.5	7.8	5.4	132	55
695	F	20	2	Cat.	0	++	..	..	6.4	0.9	4.4	0.6	1.8	0.9	8.0	5.3	115	65
1602	M	33	60	S.	0	++	26	4	6.6	1.1	4.3	0.7	2.2	0.4	12.4	1.8	223	43
1999	F	33	14	Br. S.	0	+	20	8	6.3	0.9	4.3	0.8	1.9	0.2	11.0	2.0	190	46
1713	F	15	1	Cat.	0	+	21	6	6.4	0.7	4.7	0.3	2.0	0.2	6.4	4.4	131	55
1769	M	22	2	C. E.	0	++	25	29	7.1	1.0	4.5	0.5	1.8	1.3	10.4	3.5	138	41
1299	F	28	35	Cat.	0	++	19	10	6.0	1.2	4.1	1.1	1.7	0.7	9.8	1.9	172	55
2009	M	29	72	S.	+10	+	24	3	7.0	0.4	4.8	0.2	2.1	0.3	9.6	1.6	159	34
1384	M	22	24	C. E.	+11	++	28	9	6.5	3.6	4.5	0	1.9	0.4	6.2	0.8	85	60
930	M	27	36	S.	0	+	24	11	6.3	0.2	4.9	0.1	1.5	0	8.8	1.0	161	17
1974	F	29	24	Cat.	+14	++	21	7	6.5	1.8	4.0	1.4	2.2	0.6	10.2	3.0	145	73

TABLE 2.—*Variations in Nonprotein Nitrogen, Proteins and Lipoids in Manic-Depressive Patients*

Patient No.	Sex	Age, Yr.	Duration of Illness, Mo.	Clinical Condition	Change in Weight, Lb.	Change in Mental Status	Blood Nonprotein Nitrogen, Mg. per 100 Cc.		Serum									
									Protein, Percentage		Albumin, Percentage		Globulin, Percentage		Fatty Acids, mEq.		Cholesterol, Mg. per 100 Cc.	
							Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference
1947*	F	35	24	Ma.	−12	+	24	17	6.3	1.5	4.4	0.7	1.8	1.5	10.6	2.0	180	48
1679	F	33	2	Ma. D.	+19	++	21	6	6.9	0.2	4.4	0.5	1.9	0.8	8.5	3.4	144	51
92589	F	16	12	D.	+56	+++	26	5	6.2	1.4	4.3	0.8	1.9	1.0	10.3	4.7	161	88
1444	F	25	3	A. D.	0	+++	..	..	6.6	1.4	4.3	1.1	2.2	0.3	12.9	1.5	180	71
1963	F	32	6	A. D.	+13	+++	26	10	6.5	1.8	4.2	1.1	2.3	0.8	11.0	6.6	119	91
2002	F	56	1	A. D.	−20	++	26	7	6.2	0.8	4.4	0.6	1.9	0.1	10.5	5.2	175	68
1568*	M	34	2	A. D.	0	+	31	0	6.5	0.7	4.8	0.7	1.6	0.3	8.3	2.5	155	20
1715	F	33	8	A. D.	0	++	..	..	6.6	1.0	4.3	0.3	2.2	0.8	13.5	2.8	274	70
1741	F	32	8	A. D.	−16	++	29	6	6.2	2.2	4.3	1.3	2.3	1.3	13.3	5.3	242	64
516	M	60	10	A. D.	0	+	..	..	6.7	0.8	3.7	0.4	3.0	0.5	11.3	3.9	186	30
1934	M	49	6	D.	0	++	25	20	5.8	1.1	3.9	0.7	2.9	0.5	17.1	7.0	223	50

* Asterisks indicate patients who were severely dehydrated.

TABLE 3.—*Variations in Nonprotein Nitrogen, Proteins and Lipoids of Patients with Conditions Intermediate Between Schizophrenia and Manic-Depressive Psychoses*

Patient No.	Sex	Age, Yr.	Duration of Illness, Mo.	Clinical Condition	Change in Weight, Lb.	Change in Mental Status	Blood Nonprotein Nitrogen, Mg. per 100 Cc.		Serum									
									Protein, Percentage		Albumin, Percentage		Globulin, Percentage		Fatty Acids, mEq.		Cholesterol, Mg. per 100 Cc.	
							Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference	Minimum	Difference
1759	F	28	1	Br. S.	+13	+++	23	14	6.1	1.6	4.1	1.1	1.5	0.6	8.1	3.5	131	63
1792	F	18	1	Br. S.	0	+	18	9	7.1	1.5	4.4	0.7	2.3	0.3	10.9	3.1	237	41
1950	M	22	7	A. D.-Br. S.	−10	++	24	10	6.1	2.0	4.2	1.5	1.7	0.3	10.2	3.6	193	81
1807	F	18	12	D.	+10	++	21	14	6.4	1.1	4.5	0.8	1.8	0.4	10.5	8.0	176	60
1958	M	31	12	Br. S.	+30	+++	20	10	5.6	1.4	3.8	1.0	1.8	0.4	8.3	5.4	137	152
1773	M	28	3	Br. S.	+20	+++	21	9	6.3	0.5	4.4	0.5	1.7	0.2	8.8	7.8	161	73
1667	F	52	24	Br. S.	−17	++	..	..	6.5	0.8	4.2	0.2	2.4	0.6	12.0	3.7	272	89

dition and later of schizophrenia, only special clinical features have been emphasized by the abbreviations in the column headed "Clinical Condition." "Br.S." indicates the presence of complex and extensive disorders of the vegetative nervous system, and in some instances of muscle tremors, disturbances of facial expression and other symptoms of involvement of the brain stem.

While 7 of the schizophrenic patients showed marked improvement, indicated by + +, and 6 a moderate degree of improvement, indicated by +, none had a good remission of symptoms while under study. One patient, 1722, who was the only person in the group with long-standing and slowly deteriorating schizophrenia, became slightly worse, and has been given the rating of — in the column labeled "Change in Condition." In contrast to the schizophrenic patients, 3 of 7 patients with the intermediate syndrome, listed in table 3, experienced good remissions (+ + +) and were able to take up their former activities in the community; 2

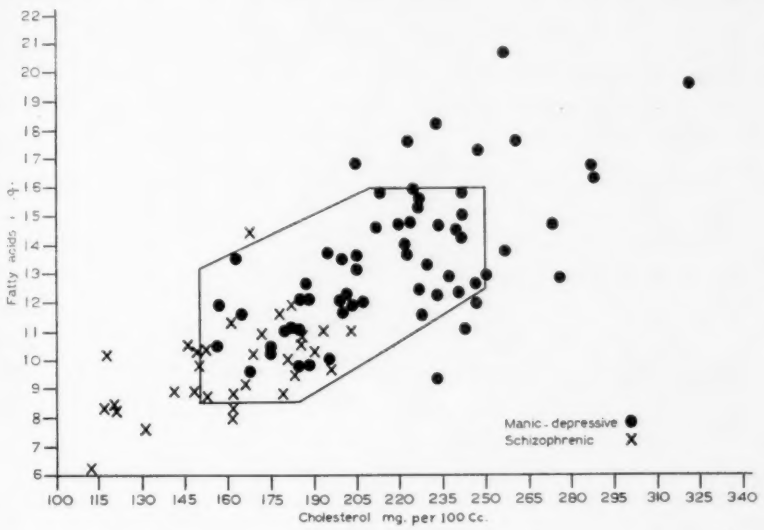

Fig. 1.—Comparison of the fatty acid and cholesterol contents of the serum in 34 schizophrenic patients (indicated by crosses) and 62 manic-depressive patients (indicated by solid circles). The hexagon includes the distribution of similarly plotted data on 73 men and women in good health (see text, page 940).

showed marked improvement for a time; 1 displayed great variation in symptoms, and only 1 improved to as slight a degree as that indicated by +. Of the patients with manic-depressive psychoses, 3 had good remissions while being studied, and 1 had three brief remissions between manic and depressive attacks. Samples of blood were not obtained at these times, however, and subsequently, during the periods of observation, she showed only a marked degree of improvement (+ +). As for the rest, 5 patients showed marked improvement (+ +) and 2 a moderate degree of improvement (+). The duration of the disease for the schizophrenic patients up to the time of the studies ranged from two months to six years, with the exception of patient 1722, who had been ill seven or more years. For the group with the intermediate syndrome the duration was from one month to two years, and for the manic-depressive patients, up to the recent attack, the time varied from one month to two years; all but 2 of the latter had had one or more previous attacks. No previous attacks were recorded for the schizophrenic patients,

and for only 1 patient with the intermediate condition was evidence of a previous break discovered.

In the cases in group 2, in which only one or two studies were made, the same care was taken in regard to the diagnoses; in addition, the cases were not included when extreme dehydration was present. The factor of undernutrition was frequently present in both the cases of schizophrenia and those of manic-depressive psychosis, and therefore tended to lower the findings for lipoids, and possibly for proteins, in each group to a similar degree.

The chief purpose of the study on the second group was to determine whether there was any difference between the level of blood lipoids in the schizophrenic and that in the manic-depressive patients, and also how much the values varied from the normal. For this purpose, the data have been plotted in figure 1. The values for fatty acids, expressed in milliequivalents, have been plotted along the ordinate, and those for cholesterol, along the abscissa. The crosses indicate the patients with schizophrenia and the black circles those with manic-depressive psychoses. The hexagon represents the distribution of normal values for 73 persons in good health when plotted in the same manner.

Table 4 gives the average values for serum lipoids in normal men and women and in schizophrenic and manic-depressive patients.

TABLE 4.—*Comparison of Average Lipoid Values in Manic-Depressive, Schizophrenic and Normal Groups*

	Male			Female			Total		
	No.	Fatty Acids, mEq.	Cholesterol, Mg. per 100 Cc.	No.	Fatty Acids, mEq.	Cholesterol, Mg. per 100 Cc.	No.	Fatty Acids, mEq.	Cholesterol, Mg. per 100 Cc.
Manic-depressive	10	13.7	201	52	13.4	223	62	13.5	219
Schizophrenic	19	9.6	160	15	10.3	171	34	9.9	165
Normal	38	12.3	195	35	12.0	201	73	12.1	198

Figures 2, 3, 4, 5 and 6 illustrate changes in symptoms, weight and fatty acid and cholesterol contents of the serum in patients 92589, 1958, 1759, 1950, 1449 and 1934.

RESULTS

The long term studies, summarized in tables 1, 2 and 3, show that the patients who underwent marked changes in their mental symptoms also had changes in the cholesterol, fatty acids and total proteins of the blood serum, and less frequently in the albumin, globulin and nonprotein nitrogen, that were beyond the limits of normal variation. None of the 14 patients with the characteristic symptoms of schizophrenia (table 1) had a complete remission. Of the 7 patients who improved markedly, all but 2 had deviations in the protein level beyond normal limits. In only 5 patients, however, did the albumin and globulin fractions deviate beyond the extreme limits of normal. The 1 patient who was deteriorating slowly suffered a marked change in the proteins and the fatty acids, and to a less extent in the cholesterol. Abnormal changes in fatty acids occurred in only 4 patients, in contrast to such changes in cholesterol in 6 patients. Five of these 6 patients were among those with a variation in the mental status of + +. Patient 1602, the exception, was jaundiced for a time, and tests showed abnormal retention of bilirubin.

As only 3 of the 11 manic-depressive patients included in this study (table 2) had a remission while under observation, the results are not as striking as were the changes in fatty acids in groups studied several years ago. However, all of

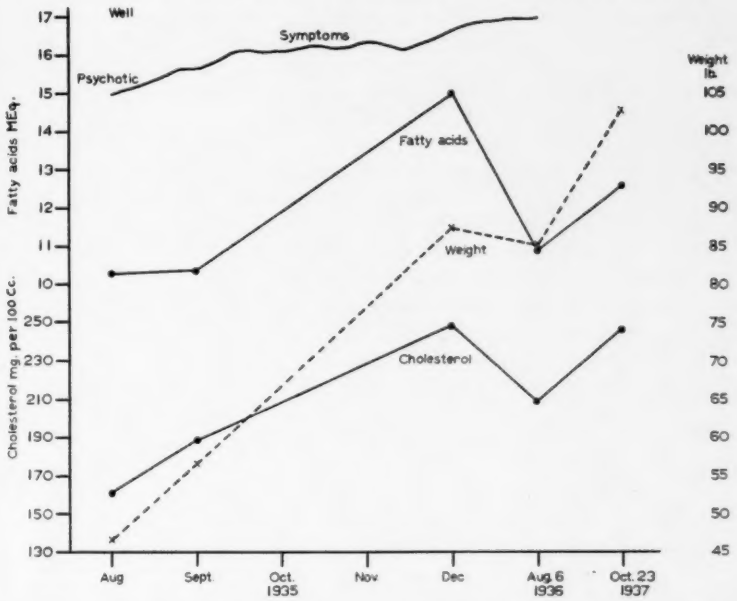

Fig. 2.—Chart showing the variations in fatty acids and cholesterol of the serum and in body weight in patient 92589 during recovery from a depression (see text, page 943).

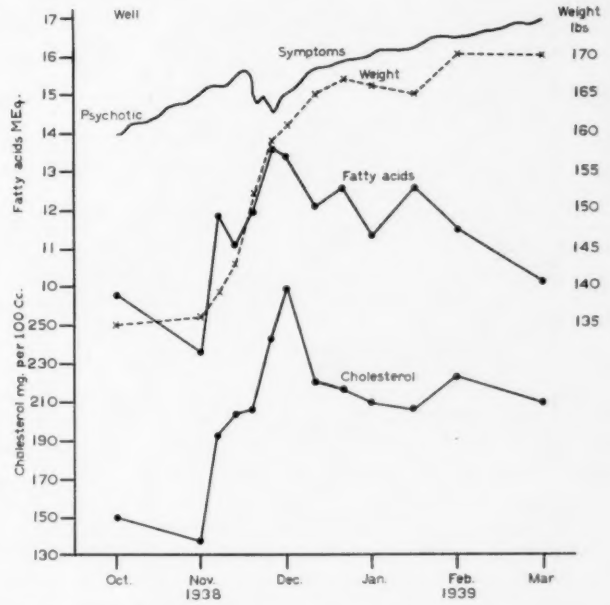

Fig. 3.—Chart showing changes in fatty acids, cholesterol and weight in patient 1958 during recovery from a psychosis in which paranoid, catatonic and depressive symptoms were shown (see text, page 943).

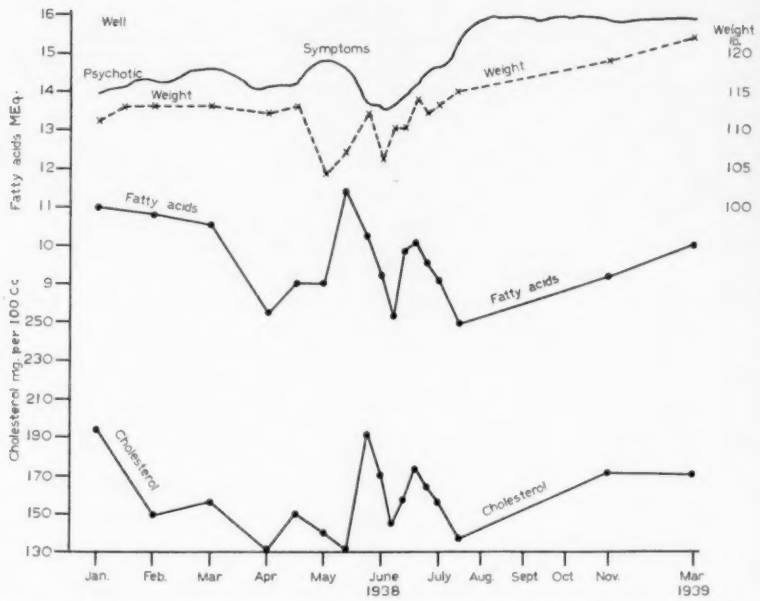

Fig. 4.—Chart showing changes in fatty acids, cholesterol and weight in patient 1759 during recovery from a psychosis showing paranoid, catatonic and depressive features (see text, page 944).

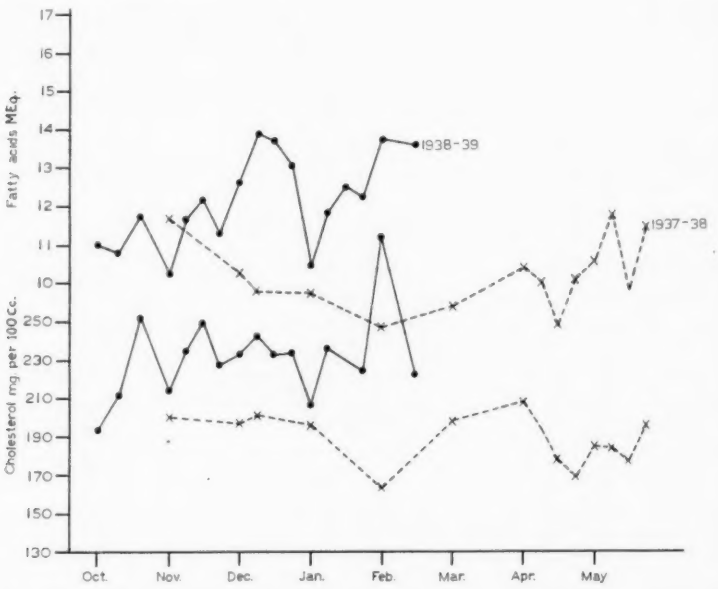

Fig. 5.—Chart showing marked fluctuations in fatty acids and cholesterol in patient 1950 (indicated by a solid line) and in patient 1449 (indicated by a broken line), whose symptoms varied markedly but showed no indication of recovery (see text, page 944).

the 8 patients who had a change in condition of either + + or + + + showed significant changes in one or both of the lipoid components. Six of these 8 patients had abnormal variations in the total proteins. Patient 1947, with manic excitement and only moderate fluctuations in her condition, had practically normal variations in cholesterol and fatty acids, and the abnormal change in proteins and nonprotein nitrogen was associated with extreme dehydration that arose from her temporarily successful resistance to being fed.

Three of the patients with the intermediate syndrome (table 3) had good remissions, while 4 others showed marked fluctuations in symptoms. It is noteworthy that all these 7 persons had variations in cholesterol that were well beyond normal limits. All but 1 of these patients had nonprotein nitrogen values which were beyond normal limits, while with 2 exceptions the variations in proteins

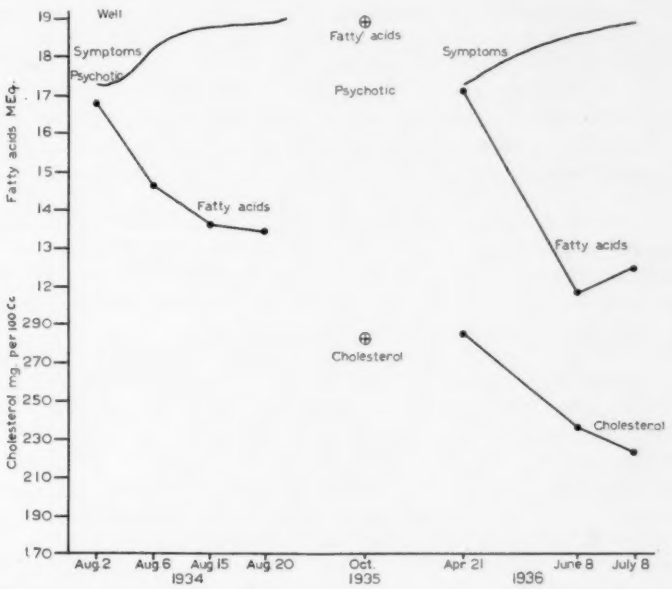

Fig. 6.—Chart illustrating variations in fatty acids and cholesterol in patient 1934 during three successive attacks of depression and agitation.

were abnormal. It is of interest that the remaining patient, no. 1792, who had a moderate change in mental status (+), showed only a marked change in total proteins, associated with dehydration, while the other constituents varied within the normal range.

Most of the patients showed fluctuations in weight while being studied, but in only 2, patients 92589 and 1958, were they of sufficient magnitude, that is, more than 15 per cent of that when well, to be considered as certainly affecting the level of the serum proteins and lipoids. Patient 92589 (fig. 2) in the course of a depression lost 55 per cent of her normal weight. During the period of study she made a complete recovery to a mild hypomanic level, gaining slightly more in weight than she had lost. This extreme change in nutritional status probably obscured any changes that occurred in the lipoids and proteins. The other patient (no. 1958, fig. 3) in the group with the intermediate condition regained 19 per cent of her body weight during recovery.

Figure 4 illustrates the variations in fatty acids and cholesterol in patient 1759. Her illness developed acutely, with rapid variations from an agitated and depressed state to a catatonic condition and paranoid delusions. Progress took place with remissions and exacerbations, ending with good recovery. It can be seen that although the line denoting severity of symptoms does not exactly follow the change in lipoids, a relation appears to exist. On her admission in January 1938, the lipoids were high, in spite of a recent loss in body weight of 10 per cent, and the patient showed severe symptoms of panic, agitation, depression, self-accusatory ideas and vivid paranoid delusions. A partial remission occurred, during which the lipoid level declined. Then a moderate exacerbation in April was accompanied by a rise in lipoids. Another remission occurred, and then, between May 17 and 24, a severe exacerbation and a rise in the lipoid level to that at admission took place. The subsequent recovery was accompanied by a fall in lipoids, while part of the original weight was regained. The patient did well after leaving the hospital and gained in weight; at the same time she became slightly overactive and remained a little tense. During this time a slow rise in lipoids occurred.

Figure 5 shows the fatty acid and cholesterol values for 2 patients (no. 1950, with the intermediate syndrome, and no. 1449, with catatonic schizophrenia) who manifested marked fluctuations in symptoms but did not recover. In general, the acutely disturbed periods coincide with the peaks in the lipoid levels. The weight of both patients fluctuated within a range of 6 pounds (2.7 Kg.).

Figure 6 illustrates variations in the lipoids in a patient during three attacks of depression and agitation over a period of three years. Changes in weight amounted to only 6 pounds during recovery, and therefore did not introduce a complicating factor. It can be seen that the lipoids were high when the symptoms were severe and that they fell with recovery.

The comparative study of cholesterol and fatty acids in 34 schizophrenic and 62 manic-depressive patients, as presented in figure 1, indicates that the former had considerably lower values for lipoids than most of the latter. In all the schizophrenic patients the cholesterol fell below 200 mg. per hundred cubic centimeters and the fatty acids, with 1 exception, below 12 milliequivalents. In all but 2 of the schizophrenic patients cholesterol and fatty acids were below the normal means of 198 mg. per hundred cubic centimeters and 12.1 milliequivalents, respectively. Furthermore, as summarized in table 4, 48 of 62 manic-depressive patients showed figures above the average normal levels for both lipoid constituents and none below the low limits of normal. It is also noteworthy that about 30 per cent of the schizophrenic patients showed figures below, and 23 per cent of the manic-depressive patients figures above, the limits of normal for cholesterol and fatty acids, as indicated by the hexagon in figure 1. Sex, age and physique did not appear to play an important part in determining these differences.

COMMENT

The long term studies on the schizophrenic patients revealed abnormal variations in serum lipoids and proteins in those whose clinical status changed in a striking manner during the period of study. In the 6 patients whose clinical status did not fluctuate so much, the variations tended to fall within normal limits, 3 patients having values within normal limits for the six metabolic constituents, 2 having only one variable and the other two variables beyond these limits.

From these data one would conclude that the metabolic variations occur chiefly in the active, shifting phases of schizophrenia and that one would not expect to find them once the chronic phase had been reached.

However, it appears that the Worcester group of investigators has found in their extensive studies that some metabolic substances continue to show abnormal variations even in the more chronic and settled phases of schizophrenia. It should also be noted that 8 of our patients presented some catatonic features, and that they therefore showed greater and more rapid changes in condition than would commonly be found in other forms of schizophrenia. Although 7 of our patients had symptoms of marked disorder of the vegetative nervous system and certain other symptoms of disturbance of the hypothalamus and the brain stem, the values for serum lipoids were not high; this constituted a marked contrast to the other values for other groups of patients with similar, but more severe, evidences of dysfunction of the brain stem.

A comparison of the data on the schizophrenic patients with those on the patients with the intermediate syndrome indicates that patients with disturbances in mood and energy as well as features of schizophrenia had higher lipoid values and that variations in these substances were more marked. This marked variation did not occur, however, unless there was a marked change in mental status. It is also noteworthy that symptoms of dysfunction of the brain stem were more marked in this group than in the group of patients with relatively uncomplicated schizophrenia.

The patients with manic-depressive psychosis showed variations similar to those of patients with the intermediate type of illness. Again, when the clinical status did not change the variations in the constituents of the blood were rarely beyond normal limits. The case of patient 516, aged 60, constitutes a good illustration of this absence of variation. He was in a severely depressed and continually agitated state during the six months of study and showed little variation in symptoms and correspondingly slight fluctuations in proteins and lipoids.

The evidence that the changes in lipoids are related in some way to the mental disorder has been secured by following patients during remissions and exacerbations of their symptoms. That the fatty acid content of the serum is elevated in manic-depressive patients during the illness and falls with recovery was reported by us at a meeting of the American Psychiatric Association in 1934. These observations have been supplemented by further studies, and it has been found that this trend takes place in cholesterol as well as in fatty acids, provided it is not obscured by extreme changes in weight. The observations are well illustrated by patient 1934 (fig. 6), who had a marked increase in fatty acids and, to a less extent, in cholesterol during each of three attacks of agitated depression in successive years. The lipoids fell with recovery from the depression. The patient lost and then gained only 5 to 6 pounds (2.3 to 2.7 Kg.) in these cycles, and therefore the change in weight was not sufficient to be a factor. A comparison of the values for patient 1934

with those for patient 92589, which are shown in figure 2, illustrates the dominant effect of severe nutritional disturbances. Patient 92589, in the course of a depression, gave up eating and lost 55 per cent of her body weight. After admission to the hospital, feeding with a spoon and partial remission in symptoms were followed by a rapid rise in the serum lipoids. In this patient severe depletion of all tissue lipoids by starvation made impossible any elevation of serum lipoids which might otherwise have taken place as a result of the disorder of the nervous system. In figure 4 are illustrated the variations in lipoids with remissions and exacerbations in symptoms and fluctuations in weight for patient 1759, who showed a mixture of catatonic and depressive symptoms as well as paranoid delusions, and who finally recovered in a manner similar to that exhibited in a classic manic-depressive psychosis.

The aforementioned findings are similar to those in the lipoid studies of Stenberg,[12] who concluded that states of marked emotional tension are associated with elevation of lipoids both in schizophrenic and in manic-depressive patients.

Except in the cases of 2 manic-depressive and 2 schizophrenic patients, dehydration was not sufficient at the time the studies were made to affect seriously the results. Furthermore, 2 of these subjects were patients who did not show abnormally great variations.

Abnormal variations in the nonprotein nitrogen of the blood and in the proteins and albumin of the serum were observed in both schizophrenic and manic-depressive patients. The changes in proteins were not all due to the albumin fraction alone; in some patients the globulin varied more than the albumin. We are uncertain in regard to the interpretation of the data for albumin and globulin because many of the changes which were not accepted as sufficient to be called abnormal in this study have been described as indicative of hepatic dysfunction by previous investigators. This difficulty has arisen from the fact that 1 of the healthy male subjects showed a fall in albumin amounting to 1.2 per cent on one occasion and that a healthy woman approximated this degree of change. It should be noted, however, that 10 other control subjects, who were studied for a much longer period, showed changes that were below 0.86 per cent. As the method is subject to occasional unexplainable variations that make it impossible to obtain checks of duplicates, we hesitate to lay stress on any but large changes in albumin as being abnormal. Other evidences of hepatic dysfunction were not found in any of the patients, except patient 1602, who had jaundice and showed retention of bilirubin when tested. However, the more delicate tests of hepatic disorder, such as the hippuric acid test of Quick, were not

12. Stenberg, S.: Psychosis and Blood Lipoids: Quantitative Variations of Total Cholesterin and Total Fatty Acids in the Blood in Dementia Praecox, Acta med. Scandinav. **72**:1, 1929.

employed. The changes in nonprotein nitrogen and proteins are probably merely the reflection of the more fundamental changes demonstrated in the balance studies on patients with catatonic stupor by Gjessing.[5] In view of the aforementioned findings, we suggest that Gjessing might have found disturbances in protein metabolism in manic-depressive patients similar to those in catatonic persons if he had studied complete cycles.

The observation that the manic-depressive patients as a group had higher, and the schizophrenic patients lower, values for lipoids than the normal subjects is of particular interest in connection with the previous studies of Gildea, Kahn and Man [7] showing the relation between blood lipoids and such pyknophilic features as pyknic habitus and high energy output. In the present study too large a proportion of the patients had physiques that were neither pyknic nor leptosomic to warrant any attempt at correlation on the basis of body build. The fact that not many persons in this study had an extreme pyknic habitus indicates, however, that high lipoid levels occur in manic-depressive patients even when external morphologic features are not clearly pyknic and in spite of the common occurrence of a loss in weight of more than 10 per cent.

These findings lend further support to the hypothesis that high values for serum lipoids can be used as a measure of the pyknophilic qualities that go to make up the particular kind of person who is predisposed to a manic-depressive condition. Furthermore, low lipoids may be taken as indicating leptophilic qualities, which, as the data suggest, are commonly found in persons who are leptosomic in habitus, have low energy reserves and are predisposed to display schizophrenic symptoms.

CONCLUSIONS

Long term studies of 14 patients with schizophrenia, 11 with manic-depressive psychoses and 7 with symptoms of both conditions revealed abnormal variations in the nonprotein nitrogen of the blood and in the total proteins, cholesterol and fatty acids of the serum in all the persons who showed marked changes in clinical status. The patients whose symptoms showed little change rarely had abnormal variations in these constituents.

These results demonstrate that there are abnormally large metabolic changes in the blood which accompany the variations in mental symptoms, particularly those symptoms which can be attributed to dysfunction of the brain stem. When changes in nutritional status were not extreme, the serum lipoids rose during the manic or the depressed phase of the illness and fell with recovery.

Manic-depressive patients as a group were found to have high cholesterol and fatty acid values, while, in contrast, the schizophrenic patients had lipoid values that were below the normal average, in many instances being below the normal limits.

HISTOLOGIC CHANGES FOLLOWING METRAZOL CONVULSIONS

WITH NOTE ON A FUCHSINOPHILIC REACTION AS AN INDEX OF EARLY NEUROCYTOLOGIC CHANGE

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The purpose of the present study was primarily to obtain information concerning the effects of metrazol in doses sufficient to produce seizures, or of the seizures themselves, on the brain and its vascular supply.

Thousands of psychiatric patients [1] have already been subjected to metrazol therapy. At present it is being employed in treatment of a large and increasing number of schizophrenic patients and, less widely, of patients with affective psychoses,[2] psychoneuroses [3] and other personality problems.[4]

Apparently, the dangers of death from this heroic regimen are relatively slight.[5] Judged by clinical standards, patients who have been extensively treated do not often show evidence of organic damage to the brain.[6] Physical complications independent of neurologic damage are, of course, well known; dislocations,[7] fractures of the long bones,[8]

From the Departments of Neuropsychiatry and Anatomy, the University of Georgia School of Medicine and University Hospital.

1. Friedman, E., and von Meduna, L.: The Convulsive-Irritative Therapy of the Psychoses, J. A. M. A. **112**:501-509 (Feb. 11) 1939.

2. Bennett, A. E.: Convulsive (Pentamethylenetetrazol) Shock Therapy in Depressive Psychoses: Preliminary Report of Results Obtained in Ten Cases, Am. J. M. Sc. **196**:420-428 (Sept.) 1938.

3. Low, A. A.; Sonenthal, I. R.; Blaurock, M. F.; Kaplan, M., and Sherman, I.: Metrazol Shock Treatment of the "Functional" Psychoses, Arch. Neurol. & Psychiat. **39**:717-736 (April) 1938.

4. Owensby, N. M.: Convulsive Therapy in Mental Disorders, South. M. J. **31**:1164-1166 (Nov.) 1938.

5. Kennedy, A.: Convulsive Therapy in Schizophrenia, J. Ment. Sc. **83**:609-629 (Nov.) 1937. Friedman and von Meduna.[1] Low and others.[3]

6. Low, A. A., in discussion on Weil and Liebert.[15]

7. (*a*) von Meduna, L.: Die Konvulsiontherapie der Schizophrenie, Psychiat.-neurol. Wchnschr. **37**:317 (July) 1935. (*b*) Winkelmann, N. W.: Metrazol

temporary auricular fibrillation,[9] laryngeal spasm[10] and compression fractures of the vertebral bodies[11] have been reported. The apparent efficacy of the metrazol convulsive therapy is indeed encouraging and would perhaps justify its use in cases of schizophrenia even if the mortality were much higher.

The possibility of irreversible injuries to the brain in severe and repeated convulsive seizures readily suggests itself. It is commonly believed that the similar seizures in epilepsy contribute substantially to the familiar intellectual and emotional deterioration often found in that condition.[12]

Some observers have reported the absence of histopathologic changes in experimental animals in which seizures were produced by administration of metrazol. Stender,[13] working with cats and rabbits, observed slight clumping of Nissl substance in ganglion cells, slight glial proliferation and, in an immature animal, subpial hemorrhages. He concluded that the subpial hemorrhages were caused by trauma during convulsions and that none of the changes he reported indicated definite damage from direct effects of the metrazol or of the seizures. De Morsier and his associates[14] studied the brain of a rabbit which had been given nine fit-producing injections of metrazol and the brain of another rabbit killed by a massive dose of metrazol. No histopathologic changes were

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Treatment in Schizophrenia, Am. J. Psychiat. **95**:303-316 (Sept.) 1938. (*c*) Friedman, E.: The Irritative Treatment of Schizophrenia, ibid. **94**:355-372 (Sept.) 1937. (*d*) Cohen, L.: The Early Effects of Metrazol Therapy in Chronic Psychotic Over-Activity, ibid. **95**:327-333 (Sept.) 1938.

8. (*a*) Nightingale, G. S.: Six Months' Experience with Cardiazol Therapy, J. Ment. Sc. **84**:574-580 (May-July) 1938. (*b*) Goldstein, H. H.; Dombrowski, E. F.; Edlin, J. V.; Bay, A. P.; McCorry, C. V., and Weinberg, J: Treatment of Psychoses with Pentamethylenetetrazol, Am. J. Psychiat. **94**:1347-1354 (May) 1938.

9. Dick, A., and McAdam, W.: Cardiac Complications in Cardiazol Treatment: Observations in Four Cases, J. Ment. Sc. **84**:999-1001 (Nov.) 1938.

10. Barbato, L.: Metrazol Therapy in Schizophrenia, Texas State J. Med. **34**: 220-227 (July) 1938.

11. Polatin, P.; Friedman, M. M.; Harris, M. M., and Horwitz, W. A.: Vertebral Fractures Produced by Metrazol-Induced Convulsoins in Treatment of Psychiatric Disorders, J. A. M. A. **112**:1684-1687 (April 29) 1939.

12. Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937, p. 837.

13. Stender, A.: Ueber Provokation epileptiformer Anfälle durch Cardiazol (Experimentelle und histopathologische Untersuchungen an Tieren), München. med. Wchnschr. **84**:1893-1895 (Nov. 26) 1937.

14. de Morsier, G.; Georgi, F., and Rutishauer, E.: Experimental Studies of Convulsions Provoked by Cardiazol in Rabbits, Am. J. Psychiat. (supp.) **94**: 207-208, 1938.

observed in either animal. In both experiments only sections stained by the Nissl method were mentioned.

Weil and Liebert [15] reported definite histopathologic changes in the central nervous system of rabbits subjected to metrazol convulsions. These were described, however, as mild changes "consisting of shrinkage of the nuclei and cytoplasm of ganglion cells in various regions." Such changes were noted only in animals which had received a "total of 700 mg. of metrazol or more." The pathologic changes appeared to be more definitely related to the total amount of metrazol administered than to the severity or amount of convulsive activity. According to the results obtained from these animal experiments, it appeared to the observers that a total of 13.5 Gm. is the maximal cumulative dose that may be given to a patient "without producing histologically demonstrable pathologic changes in the central nervous system." The highest total amount of metrazol given to the mice in the present series (4.0 mg.) corresponds to a total amount of 12 Gm. for an average patient. Animals which received total amounts of metrazol of 2.3 and 2.7 mg., respectively, approximately proportionate to 6.9 and 8.1 Gm. for the average patient, showed marked signs of neuropathologic lesions. Strecker and his co-workers [16] reported histopathologic changes in the brains of monkeys (Macacus rhesus) which were subjected to metrazol convulsions. Of 7 animals which were given metrazol (intra-arterially), 3 died of prolonged seizures. In 3 of the 7 brains no evidence of damage was noted. Of the other 4 brains, 1 showed swelling and vacuolation of cytoplasm in cells of the external granular layer of the frontal and parietal cortex, 3 subarachnoid hemorrhage and 1 swelling of the cytoplasm and deposits of fat in the Betz cells. In 3 of the specimens changes were noted in the supraoptic nucleus, the cells showing loss of Nissl substance and vacuolation of nuclei. The animals in which histopathologic changes occurred underwent total periods of convulsive activity (the summated periods of each animal's separate fits) ranging from sixty-seven to one hundred and forty-seven minutes.

Strecker and his associates suggested that the pathologic changes may have been determined by the prolonged total period of convulsive activity, which was of greater duration than that ordinarily experienced by patients under treatment with metrazol.

None of the animals in the present experiment exhibited total convulsive activity lasting over ten minutes. Periods of milder kinetic

15. Weil, A., and Liebert, E.: Histopathologic Changes in the Brain in Convulsions Experimentally Induced with Metrazol, Arch. Neurol. & Psychiat. **39**: 1108-1110 (May) 1938.

16. Strecker, E. A.; Alpers, B. J.; Flaherty, J. A., and Hughes, J.: Experimental and Clinical Study of the Effects of Metrazol Convulsions, Arch. Neurol. & Psychiat. **41**:996-1003 (May) 1939.

activity, which occurred between seizures, when added to those of convulsive activity, bring our figures to a total of less than twenty minutes during which any of the mice described here showed motor effects of metrazol.

MATERIAL AND METHOD

In the present experiment, 10 mice were given metrazol. A varying number of seizures, which also differed widely in severity and type, were produced. Intravenous administration was not practical in animals of this size, so the drug was injected subcutaneously. Prolonged convulsive phenomena were more frequent, as one might expect, and successive seizures were not rare. Contrary to the usual reports, successive seizures have occasionally occurred in the treatment of patients.[17]

The brains of these animals and those of 2 untreated control animals which were killed by exsanguination were removed immediately after death, fixed for twenty-four hours in Huber's trichloroacetic acid fixative and then placed in 95 per cent alcohol until embedded by the diethylene dioxide (dioxane) method.

In order to avoid any disturbance of objectivity on the part of the observers, the injections were conducted by one of us, the technical work was done by a second and the examination by a third, a series of arbitrary key numbers alone being used to designate the animals.

RESULTS

The seizures and other motor activities observed in the animals were, in general, similar to effects often described as occurring in patients.[18] Motor activity, much more lively and spectacular but scarcely more violent than anything reported in man, was often observed before and after the seizure and between seizures. This might be accounted for by the slower absorption of metrazol following subcutaneous administration and the consequently longer periods of subconvulsant but excitatory effect.

Some of these manifestations were not without interest. At intervals varying from fifteen seconds to three minutes after the subcutaneous injection, the animals usually showed the effect of the drug by separate, coordinated jerks. These occurred from four to fifteen seconds apart, often causing the animal to slip backward while still maintaining its normal posture. There was no apparent disturbance of awareness or sign of confusion. The effect suggested a clownish dance step, consisting of sudden retropulsion with a concomitant, upward jerk of the head. This phase lasted for periods varying from four or five seconds to several minutes. Occasionally it was entirely absent.

Suddenly, disrupting this process, the major fit occurred. This was sometimes a clonic, sometimes a tonic, manifestation. Often both the tonic and the clonic phase were observed, but the typical sequence from tonic to clonic phase, familiar in patients treated with metrazol, was not regular. The clonic phase preceded the

17. (*a*) McAdoo, H. W.: Metrazol Convulsive Phenomena in Dementia Praecox, J. A. M. A. **110**:528 (Feb. 12) 1938. (*b*) Geeslin, L., and Cleckley, H.: Anomalies and Dangers in Metrazol Therapy of Schizophrenia, Am. J. Psychiat. **96**:183 (July) 1939. Nightingale.[8a]

18. Finkleman, I.; Steinberg, D. L., and Liebert, E.: The Treatment of Schizophrenia with Metrazol by Production of Convulsions, J. A. M. A. **110**: 706-709 (March 5) 1938. Kennedy.[5] Low.[6]

tonic as often as the reverse. Often the two types of seizures occurred a minute or more apart, apparently being separate and distinct manifestations rather than phases of a single seizure. The major seizures, whether tonic or clonic, lasted usually from ten to fifteen seconds, never over thirty seconds. The severe seizures were not infrequently multiple, as many as four being observed after a single injection of metrazol. Four of the 10 animals (nos. 1, 2, 7 and 8) died during or after a single major seizure. The other 6 (nos. 3, 4, 5, 6, 9 and 10) had two or more seizures preceding death.

Various other hyperkinetic phenomena were noted, in addition to those already mentioned. One of the most common of these, which occurred after almost every injection, consisted in a furious pawing or beating at the nose. This was carried out with the animal in a sitting posture, sometimes resting rather naturally on its haunches, sometimes drawn back in rigid opisthotonos. This activity was noted before and after seizures and, when multiple seizures occurred, between them. It usually lasted from ten to fifteen seconds and was sometimes carried out with extreme violence.

Before, after and between seizures the animals often darted suddenly forward, striking the wire of the cage and continuing to carry out frantic running motions, which resulted in their noses being firmly wedged into the mesh. This activity was apparently automatic, for the expressions of the animals were blank and immobile, the eyes glazed and staring.

Frequently the animals suddenly leaped straight in the air, rising from 6 to 10 inches (15 to 25 cm.) as if elevated by an explosive force. This manifestation was also noted before, after and between seizures. The leap was apparently not merely a frightened animal's purposive effort to escape. The legs jerked with stiff, convulsive violence. The effect was not that of a natural, coordinated spring but that of an involuntary motor outburst.

Occasionally the animals, in a dazed condition, bit or grasped the wire of the cage, carrying out these acts in an awkward, apparently automatic fashion.

The most frequent and striking feature noted in these varied responses was hypertonus. Nearly always, at varying intervals after the seizures or other manifestations, the animals became extremely spastic, the body gradually stiffening as if inexorably molded by a superimposed, involuntary force. While the animals were still alive, the posture hardened to the appearance of a statue, the stance usually being maintained and the tail rising slowly to a vertical position and remaining aloft like a flagpole. Rapid, shallow respiration continued while the animal remained for as long as seven minutes in this unusual state. The tail offered strong resistance to passive motion.

Some animals recovered from this state of hypertonus. It was, however, most marked preceding death. All the animals, whether dying in or after a convulsion, showed this striking general rigidity prior to, as well as in, death. The most frequent mode of death consisted in persistence and increase of rigidity, the animal dying as it stood with tail pointing in the air. Sometimes after death the body fell, but often it remained firmly in position until taken up for removal of the brain. No postmortem diminution of rigidity was noted, the corpse remaining almost as firm and hard to the touch as wood.

These hypertonic manifestations were so frequent that it was often difficult to tell whether an animal had died or was merely arrested in temporary hypertonus. Although these hypertonic manifestations sometimes ended in recovery, they usually seemed to indicate the approach of death. All the animals regularly showed lethargy and drowsiness for periods up to an hour after the convulsive or

other kinetic manifestations. Otherwise their behavior and appearance between injections were entirely normal, and they gave no impression of having suffered injury from the seizures.

As might be expected, the convulsant dose for the animals was greater proportionately than that which causes satisfactory convulsions when given intravenously to patients. If the average amount of metrazol necessary to cause a major convulsion in a patient weighing 70 Kg. is taken as 5 cc. of the usual 10 per cent solution (500 mg.), it can readily be calculated that a physiologically equivalent dose for a mouse weighing 20 Gm. would be 0.14 + mg.

It can be seen from figure 1 that 0.4 mg. sometimes failed to produce any effect, while as much as 0.8 mg. was given in some instances without causing death. A dose of 0.5 mg., it may be noted, never failed to produce a fit. A dose of 0.4 mg. produced death in 1 case. This narrow and uncertain margin of safety should not be considered as comparable to the margin between a convulsant and a lethal effect in patients who receive metrazol intravenously. The concentration of the drug in the blood stream is known to be the dominant factor in attaining the convulsions.[19] It is only reasonable to believe that the larger doses needed to cause fits by subcutaneous injection and the prolonged action may also increase the lethal effects, narrowing the margin of safety between the convulsant and the lethal dose.

It was considered desirable to compare the effects of large and immediately lethal doses with repeated convulsant but nonlethal doses. For this reason, 2 of the animals (no. 1 and 2) were given relatively enormous amounts of metrazol at the first injection. Another animal (no. 3) died after a first injection which was relatively small (0.4 mg.). In contrast to these, another animal (no. 8) showed an interval of thirty-three days between the first convulsion from metrazol and the lethal convulsion. Others, as indicated in figure 1, had varying periods between the first convulsion and death. Although all but the 2 control animals died from the effects of metrazol, a comparison, on the basis of the number and severity of convulsions and the periods over which the various animals had seizures, can be made. The question of acute histologic changes in the brain from the immediate effects of the seizure and the question of chronic effects showing themselves over several weeks as the result of repeated seizures may both be raised in the study of these specimens.

HISTOLOGIC OBSERVATIONS

It soon became apparent, in examining the experimental in conjunction with the control material, that although hemorrhage and chromatolysis were the most startling changes, it was possible on the basis of cellular degeneration and plaque formation to subdivide the material into an acute and a chronic group. While the characteristics of the tissue as a whole (gemästete astrocytes, isomorphism) had to be taken into consideration, it was found that plaques and degenerated neurocytes were generally the most reliable criteria of chronicity.

Chronic Group.—On the whole, mouse 6 showed not only the most extensive damage but also that of longest duration. A large number of plaques were present. Practically every one of these could be seen to originate about an arteriole. The arteriolar vasculature itself showed evidence of hyaline degeneration, and both the large and the small vessels were moderately constricted. Numerous large hemorrhages were present. In the cerebrum none were situated superficially, but in the cerebellum both deep and superficial hemorrhages could be seen. An area

19. Goldstein and others.[8b] Kennedy.[5]

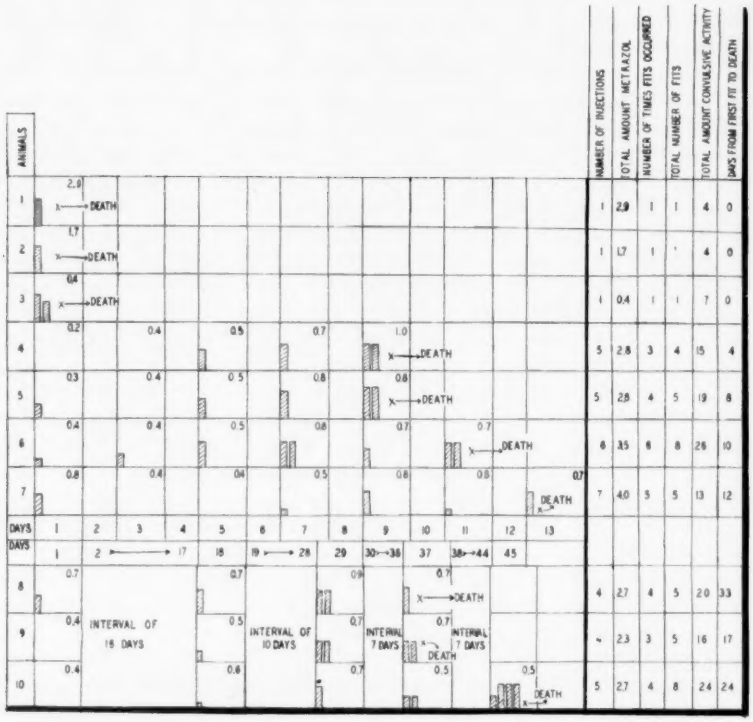

Fig. 1.—In this chart an attempt is made to represent the various factors which might determine any pathologic changes found in the brain. The number of times convulsive reactions followed administration of metrazol should, naturally, be significant. Since two or more seizures occurred after the injection on many occasions, it was necessary also to record the total number of seizures (cross hatched columns). Since the seizures varied greatly in severity, an attempt was made to represent the degree as evidenced by the duration and vigor of each reaction. This is indicated by the height of the cross hatched columns. The ratio of the slightest definite convulsive activity to the greatest is 1 : 5. Chronic changes in the brain tissue would be influenced markedly by the period during which the animal lived while having seizures. The number of days from the first seizure until death is therefore tabulated. Since some observers have found that pathologic changes varied with the total amount of metrazol administered, this figure is also given.

The data in the chart were correlated with the histopathologic observations. No signs of chronic changes were observed in the brains of animals 1, 2, 3 and 4. The first 3 mice died after the first injection of metrazol. Animal 4 died only four days after the first convulsion. Signs of acute damage were present in all of these animals.

Definite evidence of chronic neuropathologic changes were present in all the other animals. The most extensive and severe damage was noted in animal 6, which, it may be noted, underwent the greatest convulsive activity and lived for ten days before death. The next most extensive changes were found in animal 7. In each of the animals (nos. 8, 9 and 10) which had seizures over long periods plaque formation was noted. Plaques were seen in only 1 other animal (mouse 5), and here they were less numerous than in the other 3 animals.

of moderate, loose isomorphism about some of the sites of hemorrhage argued for the establishment of these hemorrhages at least several days before death. There were some loss in the number of neurocytes throughout the brain and degeneration consisting of extreme deformation of many others. Chromatolysis was pronounced. With regard to the interstitial tissue, except for the condition of the vasculature and the isomorphic changes surrounding the hemorrhagic areas previously mentioned, it should be noted that there were also present a moderate number of gemästete astrocytes.

Brain 7 showed the next most severe and long-standing damage. The number of plaques was not as great as in brain 6, but, as previously noted, the relationship between the plaques and the arterioles was incontrovertible. The vessels were generally constricted, regardless of the size, and there was perhaps a slightly greater tendency to hyalinization than in brain 6. There were present an anemic infarct and a recent, deep and massive hemorrhage, which appeared to have originated from vessels of larger caliber. Isomorphic areas and gemästete astrocytes could be seen, but not in a marked degree. There was little evidence of absence of cells, and the number of atypical neurocytes was less marked than in brain 6. Chromatolysis was pronounced.

Brains 9, 8, 10 and 5 also presented plaques in decreasing number. Brain 8 alone showed isomorphism and brain 9 alone *gemästete Zellen.* Of the 4 brains mentioned, only nos. 9 and 8 showed any hemorrhage. In brain 9 one old hemorrhage was observed in the ventral portion of the cerebrum, but there were also a number of extravasations about the larger cerebellar vessels. Brain 8 showed two hemorrhages of moderate age in the cerebrum and one in the cerebellum. In both these brains the smaller arterioles were moderately dilated, and in brain 8 this was the condition of the larger arterioles also. In brain 10 the cerebral vasculature showed some constriction, while the cerebellar vessels were slightly dilated. In brain 9 the smaller arterioles were constricted throughout. Brains 9 and 8 alone showed neurocytic loss, which, however, was slight in both cases. Some neurocytic degeneration was present in brains 9, 8 and 10, being less in the last two than in the first. Chromatolysis was notable only in brains 9, 8 and 10.

Acute Group.—Brains 2, 4, 3 and 1 showed no evidence of chronicity. Brain 3, but none of the others, showed a large recent hemorrhage. Brains 2 and 4 showed constriction of most of the vasculature, but in brains 3 and 1 only the smaller arterioles were constricted. Only brains 2 and 1 showed notable chromatolysis, and this was more severe than in any of the brains previously studied and was more marked in brain 1 than in brain 2.

It would appear that the convulsions following administrations of metrazol have the capacity of producing positive injury to the brain through vascular damage. In general, arteriolar constriction seems to be produced in the acute preparation. Such extravasations as are produced appear to take place proximal to the site of greatest constriction and seem to occur more readily after previous insult than initially. Thrombotic phenomena on a small (plaque) or large (infarct) scale appear to be of frequent occurrence. There seems to be no absolute proof of a direct effect on the neurocytes themselves other than the depletion of Nissl substance, which is frequently seen in the fatigued

Explanation of Figure 2

Fig. 2.—Photomicrographs of mouse brains following metrazol convulsions (phosphomolybdic acid-polychrome stain). The brains were immediately fixed in trichloroacetic acid, mercury bichloride U. S. P. and absolute alcohol, embedded by the diethylene dioxide (dioxane)–xylene–paraffin method and stained with acid fuchsin, phosphomolybdic acid, aniline blue and orange G. *1, 3, 5* and *6* were photographed on Wratten M plates with a transmission band of illumination from 5,100 angstroms to the red end and were developed for contrast; *2* and *4* were photographed on hypersensitive panchromatic plates and developed for low contrast. In *2* the spectral transmission band used was that just mentioned; for *4*, a band between 5,100 and 5,400 angstroms was utilized.

1 and *2* (animal 9), medullary core of cerebellum showing extravasation about the larger vessels. Note especially the region below and to the right of the larger vessels. The blood above and to the left of this vessel is located in a split in the wall. This is not a ramus. (Much larger extravasations were present in the animal but were not photographed, since they did not show the relation to the vessels so well.)

3 (animal 8), edge of an isomorphic area, with normal tissue at *A* and isomorphic tissue at *B*. Note the alteration in staining reaction in *B*.

4 (animal 6), individually altered cells having a selective staining reaction. The polychrome stain gives normally a cell in which the cytoplasm stains robin's-egg blue with purplish Nissl bodies. The cell and nuclear wall stain dark blue. The nucleus appears clear with purple granules and a bright red nucleolus. Normally several reddish granules are interspersed with the purple granules inside the nucleus but outside the nucleolus. Adjacent sections stained by the Nissl and the polychrome sections show clearly the correlation between the reactions of the two stains, but the polychrome method is more sensitive, as well as more striking, and consequently gives more widespread evidence of injury. The sequence of changes is as follows: Before the Nissl sections show any change, there is an alteration in the polychrome sections from purple to red in the perinuclear tinctorial substroma. The cytoplasm of the cells as a whole becomes more purplish. By the time a cell shows chromatolysis (by use of the Nissl technic) the polychrome stain displays the cytoplasm as red, although the nucleus may retain its normal appearance. As the cell undergoes swelling and alteration in size and shape, this condition still obtains. As shrinkage begins, there is loss in the clarity of the nucleus, which now picks up the red stain (fuchsin) and appears glassy with the polychrome stain; subsequently, the nucleolus disperses as several fine blue granules; the entire cell and its processes become red, glassy and shrunken, and the cell finally fragments. The predilection for the red coloration appears as a fuchsinophilic reaction in the first step of the staining process. This reaction appears to have much in common, if indeed it is not identical, with that elicited by the Alzheimer modification of Mann's stain, and is subject to the same limitations. Thus, it cannot be used with any but perfectly fresh material, and care must be used in handling and fixing the tissues.

5 (animal 10), dilated arteriole. Most of the smaller vessels in this brain were constricted. Many showed hyaline changes, and many were thrombotic. The larger vessels tended to be dilated; many showed the course of extravasation, and many had walls which appeared abnormal. Note in this photomicrograph the dilated perivascular space and the apparent compression of the cells to the right of the vessel (this is not a diffraction effect). Dilatation of the Virchow-Robin space may be best seen at the ventral periphery of the brain sections and looks as though the region had been forcibly dilated.

6 (animal 6), necrotic area in the course of a capillary. Many such areas were seen in those animals which lived for some time between the initial and the final convulsion. They always occurred at the tips of thrombotic capillaries. In the more chronic preparations they were succeeded by plaque formation, which apparently required about a week. Occasionally secondary hemorrhage into them was seen to occur.

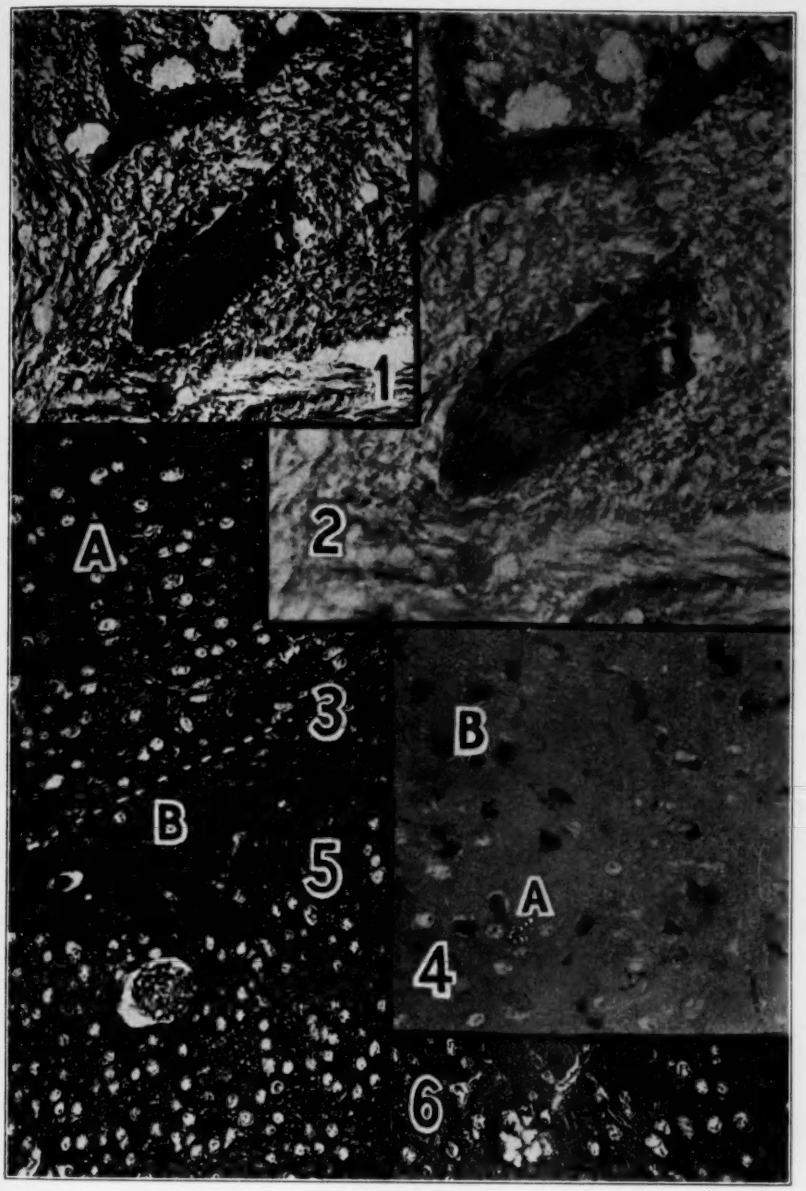

Figure 2

animal. It must be borne in mind, however, that since cytologic changes amounting to cell death did occur it is possible that such an effect may be primary, and not secondary, to vascular damage.

In many respects the changes seen in the chronic mouse group here presented are like those observed in the brains of epileptic patients, but of a much earlier type.

It is of some significance from the standpoint of neuropathology to encounter plaque formation within eight days after cerebral insult. As nearly as we are aware, this is the earliest period reported for plaque formation. It is also worth emphasizing that practically all the plaques noted in our material could be shown to be related to arterioles, a relationship sometimes mentioned [20] but often regarded as unusual.

CORRELATION AND COMMENT

It is evident that convulsant doses of metrazol produced demonstrable lesions in the brains of these experimental animals. It is also evident, from the type of lesions observed in some of the specimens, that such changes occurred prior to the lethal dose and therefore were caused by doses which induced convulsions without producing death. The duration and severity of these nonlethal seizures did not impress us as being more drastic, on the whole, than some reactions seen clinically, though the manifestations often varied from those seen in patients. Such observations suggest that demonstrable and irreversible pathologic changes probably occur also in patients despite the lack of clinical evidence denoting damage to the brain.

Even if such changes do occur regularly in patients, it may be argued that practical clinical benefit is a more valid criterion of the worth of the treatment than lesions that may be observed at autopsy. Such probable damages are scarcely to be regarded as seriously as the certain and intentional destruction of cerebral tissue accomplished in prefrontal lobotomy, with, according to some reports at least,[21] good and justifiable results. One might argue that in cases of severe personality disorders, such as schizophrenia, disruption of the currently functioning patterns of cerebration, whether these are fundamentally determined by the whole organism's methods of adaptation ("psychogenic") or by visible

20. Biggart, J. H.: Pathology of the Nervous System, Baltimore, William Wood & Company, 1936, p. 211.

21. Moniz, E.: Tentatives opératoires dans le traitement de certaines psychoses, Paris, Masson & Cie, 1936. Freeman, W., and Watts, J. W.: Prefrontal Lobotomy in Agitated Depression, M. Ann. District of Columbia **5**:326-328 (Nov.) 1936. Watts, J. W., and Freeman, W.: Psychosurgery: Effect on Certain Mental Symptoms of Surgical Interruption of Pathways in the Frontal Lobe, J. Nerv. & Ment. Dis. **88**:589-601 (Nov.) 1938.

anatomic changes in the tissues ("organic"), is desirable, whatever means one takes to accomplish it, so long as the patient is benefited.

When scar tissue following a severe burn causes contractures binding a limb or disfiguring the face, the surgeon does not hesitate to cut out the tissue which is interfering with normal function or with happiness. Sometimes, as in tenotomies, a sound and healthy part of the body is severed in an attempt to restore form or function which has been compromised by remote pathologic lesions. One is forced to the conclusion, however, that irreversible changes in brain tissue indicate drastic therapy and should, therefore, not be attempted except in very serious conditions, and then not lightly.

The states of extreme hypertonus observed in these animals, apparently signifying a dangerous and critical condition, led us to conclude that persistent hypertonus in patients treated with metrazol should be regarded as a sign of danger. Such manifestations have been observed in patients, and, in 1 case at least,[17b] they closely approximated the agonal reactions in the experimental animals noted here.

It may be argued that such findings as those noted here do not necessarily occur in man merely because they occurred in mice. A further point may be made that convulsions caused by subcutaneous injections of metrazol may affect the brain tissue in ways different from those caused by intravenous injections. While these arguments may be sound, they are not necessarily true. The present findings tend to confirm Cobb's expressed opinion [22] that metrazol therapy should be undertaken only in conditions demanding serious measures.

SUMMARY AND CONCLUSIONS

Seizures and other motor activities produced in a series of experimental animals by injections of metrazol were observed and recorded.

In contrast to the experience of some other observers,[7b, c] serious lesions were found in the brains of all animals in this series which underwent convulsions from metrazol. Strong evidence of chronic neuropathologic lesions, in contrast to changes which might be imputed to lethal seizures only, was observed in animals which had seizures over periods of more than eight days. The degree and extensiveness of the lesions in these experimental animals corresponded in general with the number and severity of the seizures observed. The type of damage to the brain seemed to be influenced by the length of time during which the animal had seizures.

In the brains of these animals the phosphomolybdic acid-polychrome stain showed a clear correlation with the Nissl stain. The polychrome

22. Cobb, S.: Review of Neuropsychiatry for 1938, Arch. Int. Med. **62**:883-899 (Nov.) 1938.

method appeared, however, to be more sensitive, showing the changes more definitely and vividly and making it possible to detect early pathologic changes more effectively. With the polychrome stain many changes in the nerve tissues which did not appear with the Nissl stain could be noted.

The total convulsive activity experienced by the animals in this experiment was considerably less than that experienced by many patients clinically and much less than that experienced by the monkeys in the report of Strecker and his associates.[16] The point made by Strecker and his co-workers that perhaps the damage to the brain which they observed could be related to the prolonged total duration of convulsive activity (a much greater total convulsive period than that experienced by patients under treatment) does not apply therefore in the present experiment.

No direct relation between the degree of neuropathologic change and the total amount of metrazol administered, as noted by other observers,[15] can be established in the present experiment. Of course, the total amount of metrazol administered bore some relation to the number of convulsions produced, but when these figures diverged the pathologic changes tended to follow the number, duration and severity of the convulsions rather than the amount of the drug.

The lesions observed in the experimental animals consistently appeared to be secondary to vascular constriction or vascular changes. This might be taken as an indication that the seizure itself is induced by vascular spasm and consequent anoxia rather than by direct influence of metrazol on the neurons.

The consistency with which lesions were produced in the experimental animals strengthens the natural suspicion that serious neuropathologic changes of some sort may occur clinically in metrazol therapy.

Many kinetic activities besides seizures were observed. Some of these were similar in various degrees to the preliminary clonic activities and torsion spasms observed in patients. Others bore little resemblance to anything seen in clinical treatment with metrazol. Persistent hypertonus was seen prior to death in every one of the animals. It is believed that persistent hypertonus is a grave sign when seen clinically.

Although the present findings tend to indicate that metrazol therapy is drastic, they should not be regarded as discrediting such treatment of conditions serious enough to warrant drastic, or even dangerous, measures.

TEMPORARY ARREST OF THE CIRCULATION TO THE CENTRAL NERVOUS SYSTEM

II. PATHOLOGIC EFFECTS

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AND

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In a preceding article,[1] the symptomatic effects of temporary complete interruption of the blood flow to the central nervous system were reported. The following report deals with the pathologic changes occurring in the central nervous system of 12 cats subjected to varying periods of circulatory arrest and killed from two days to six weeks later. The material to be presented is thought to be of interest for two reasons. First, it deals almost exclusively with the late permanent neuropathologic changes, and not with the earlier evidences of injury, which may be reversible. Second, the experimental method employed permits an accurate correlation between the late pathologic changes and the time of the circulatory arrest. Reviews of the neurologic changes produced by anemia of the central nervous system have been published by de Buck and de Moor,[2] Gomez and Pike,[3] Cannon and Burkett,[4] Gildea and Cobb [5] and Tureen.[6] In this communication earlier work will be referred to only in relation to the two points mentioned.

Aided by a grant from the Josiah Macy Jr. Foundation.

From the Harrison Department of Surgery, University of Pennsylvania Schools of Medicine.

1. Weinberger, L. M.; Gibbon, M. H., and Gibbon, J. H., Jr.: Temporary Arrest of the Circulation to the Central Nervous System: I. Physiologic Effects, Arch. Neurol. & Psychiat. **43**:615 (April) 1940.

2. de Buck, D., and de Moor, L.: Lésions des cellules nerveuses sous l'influence de l'anémie aiguë, Névraxe **2**:2, 1901.

3. Gomez, L., and Pike, F. H.: The Histological Changes in Nerve Cells Due to Total Temporary Anemia of the Central Nervous System, J. Exper. Med. **11**:257, 1909.

4. Cannon, W. B., and Burkett, I. R.: The Endurance of Anemia by Cells of the Myenteric Plexus, Am. J. Physiol. **32**:347, 1913.

5. Gildea, E. F., and Cobb, S.: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

6. Tureen, L. L.: Effect of Experimental Temporary Vascular Occlusion on the Spinal Cord: Correlation Between Structural and Functional Changes, Arch. Neurol. & Psychiat. **35**:789 (April) 1936.

Many of the morphologic changes observed in nerve cells within a few hours after a period of anemia are reversible.[7] Tureen [6] reported excellent pathologic studies on the effects of anemia on the spinal cord and demonstrated that nerve cells which apparently show many of the criteria of advanced degeneration may recover both function and normal morphologic appearance. He subjected the spinal cord to fifteen minutes of anemia, since this was found to be the longest period compatible with the return of motor function. The pathologic reaction was at its height forty-two hours after the period of anemia, although at this time the animals had completely recovered motor function. On the fifth day the nerve cells were nearly normal in appearance, and on the eleventh day no difference could be made out between the control and the experimental material. Thus it is difficult, if not impossible, to predict the permanent sequelae from the morphologic appearance of the cells shortly after a period of injury from anemia. Most of the pathologic work which has been reported deals with these early neuropathologic changes. Most of the changes described in this paper were observed several weeks after the injury.

As was indicated in the first paper of this series, most of the methods of producing temporary anemia of the central nervous system have not yielded precise results which could be duplicated because the anemia was generally incomplete. Tureen's work on the spinal cord, however, is not open to this criticism, nor is the recent work of Dennis and Kabat [8] on cerebral anemia. With the latter exception, all the work on cerebral anemia has given variable results because of the incompleteness of the anemia produced.

METHOD

The method used in the experiments reported here has been previously described in detail.[1] Briefly, it consisted of the abrupt arrest of the circulation of blood to the entire body by occluding the pulmonary artery with a clamp. After varying intervals the clamp was removed and the circulation of blood reestablished. The reappearance of blood flow in the retinal vessels was taken to indicate the end of the period of cerebral circulatory arrest. After the interval of circulatory arrest the surviving animals were observed for varying periods and then killed for pathologic study.

The animals were killed without anesthesia by the injection into the heart of 50 cc. of a dilute solution of formaldehyde U. S. P. (1:10) made neutral. The brain and spinal cord were immediately removed. In a few instances these structures were removed shortly after natural death, and before autolysis had occurred. The tissue was fixed in a dilute neutral solution of formaldehyde U. S. P. (1:10) for from four to seven days. The brains, from the frontal lobes to the medulla,

7. Hill, L., and Mott, F. W.: The Neurofibrils of the Large Ganglion Cells of Motor Cortex of Animals in Which the Four Arteries Have Been Ligated, Proc. Physiol. Soc. London, 1906, p. iv. Tureen.[6]

8. Dennis, C., and Kabat, H.: Behavior of Dogs After Complete Temporary Arrest of the Cephalic Circulation, Proc. Soc. Exper. Biol. & Med. **40**:559, 1939.

were sectioned coronally in slices from 6 to 8 mm. thick. Representative blocks were taken from various levels of the spinal cord. A few slices were kept for frozen sections, and the remainder of the tissue was embedded in paraffin. The Weil modification of the Pal-Weigert stain, cresyl violet and Mallory's phosphotungstic acid hematoxylin method were employed. A number of sections were stained by Masson's trichrome method. The frozen sections were stained with scarlet red. Serial sections were not made. Sections of the spinal cord of all the animals were studied, but no pathologic changes were observed, even in the cats with severe cerebral injury. The brains of 2 normal cats, similarly fixed and stained, were used as controls.

RESULTS

In table 2 of the preceding paper [1] the experiments are listed in order of increasing periods of circulatory arrest. The somewhat arbitrary groups have been retained to facilitate discussion of the results.

GROUP 1.—Circulatory arrest: Two minutes to three minutes and ten seconds.

The animals in which the circulation was arrested for two minutes were clinically normal within a few hours after the experiment. The brains removed from these animals showed no changes that could be considered as definitely abnormal. Sections from these brains were compared with those from the control brains, but no significant and unequivocal differences could be demonstrated. Diffuse cortical injury was seen in cat 6, 1 of the 2 animals in which the cerebral circulation was interrupted for three minutes and ten seconds. This cat was killed at the end of six weeks, at which time the animal did not exhibit any neurologic signs or symptoms or abnormalities of behavior.

A description of sections of the brain of cat 6 follows: There were no areas of softening or cortical disintegration. The splenial, suprasplenial and lateral gyri were slightly shrunken, and the intrahemispheric fissure was widened. In these gyri (fig. 1) the cortical cytoarchitecture was considerably disturbed by diffuse and patchy loss of cells, altered polarity of many of the remaining cells and the presence of large numbers of shrunken, pyknotic cells. The axons were pointing in all directions. Many granular, crumbling forms were seen, and a number of shadow cells, surrounded by satellitic glial nuclei, were noted. There was mild diffuse glial reaction. The greater part of the degeneration and cellular loss was seen in laminas III, IV and V. In the orbital, temporal and olfactory cortical areas the cytoarchitecture was well defined, and there was only slight loss of cells. There were, however, many scattered pyknotic cells. The majority of the ganglion cells appeared morphologically normal. The basal nuclei, cerebellum and brain stem were normal.

GROUP 2.—Circulatory arrest: Three minutes and twenty-five seconds to five minutes and forty-five seconds.

The cats in this group showed evidence of neurologic damage immediately after the period of circulatory arrest. Recovery was rapid, however, and, with the exception of cat 20, motor function was intact in all the animals at the time of death. Cat 20 showed some weakness

and spasticity and absence of hopping and placing reactions in the hindlegs when killed on the fifth day. All the cats in this group, however, were apathetic and indifferent to noxious stimuli, and intelligence appeared to be definitely impaired.

A description of the brain of cat 22 follows: Gross inspection of the Pal-Weigert sections revealed a small stripe of necrosis under the sulcus lateralis and

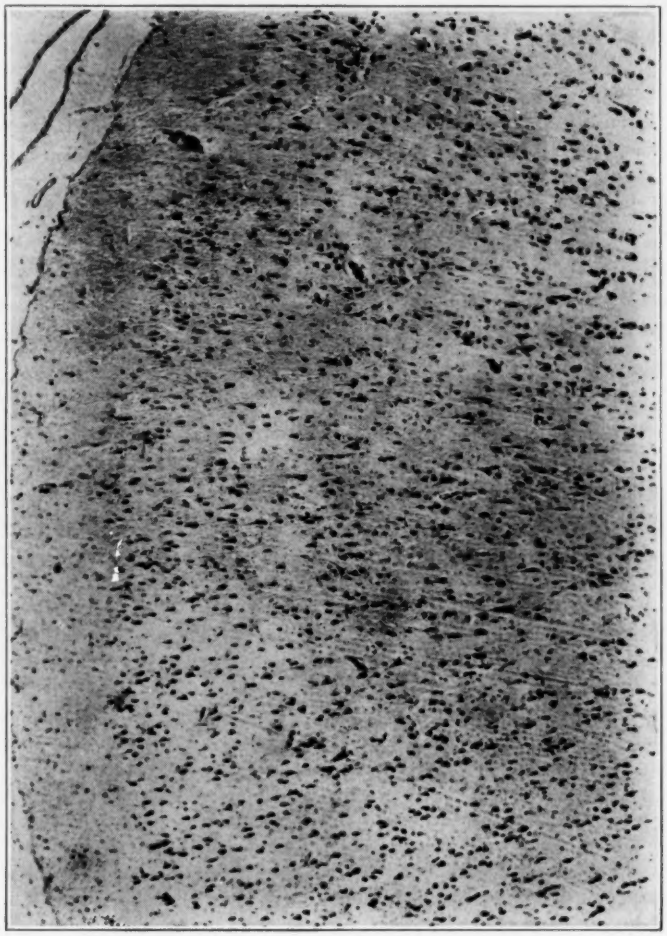

Fig. 1.—Section of cortex from the gyrus lateralis of cat 6. Cresyl violet stain. There are scattered foci of cell loss as well as diffuse diminution in the number of cells. The cortical cytoarchitecture is disturbed, and most of the ganglion cells are dark, pyknotic and shrunken.

extending into the gyrus lateralis and the gyrus suprasylvius medianus (fig. 2 *A*). A section passing through the occipital pole showed several areas of laminar and focal disintegration in the posterior lateral and splenial gyri (fig. 2 *B*). No other areas of dissolution were observed in the cortex.

Higher magnification showed that the area of necrosis involved all but the supramarginal layer (fig. 3). Its two lateral extensions involved only lamina III. Fat-laden gitter cells and swollen glia cells were present, and the number of capillaries was increased. No fibroblasts were seen, and there was no evidence of a reparative process. There were several other small wedge-shaped foci of coagulative necrosis in the same gyrus which have not yet begun to disintegrate. The occipital gyri had also undergone patchy, zonular necrosis, and a number of areas were still in a state of liquefaction. The remainder of the cortex, which had not undergone softening, showed diffuse and widespread changes, which are most intense in cortical areas 5, 6, 7, 18 and 19 and least pronounced in the orbital, rhinencephalic and temporal cortical areas. There were fewer cells than are normally present, and most of the ganglion cells showed some degree of degeneration. In the least affected gyri the laminations were preserved, and the loss of cells was not marked. Laminas III and IV were more severely injured than the other layers. Nerve cells showing the "acute cell change" were not seen. Some cells were normal in appearance; some were shrunken, amorphous and

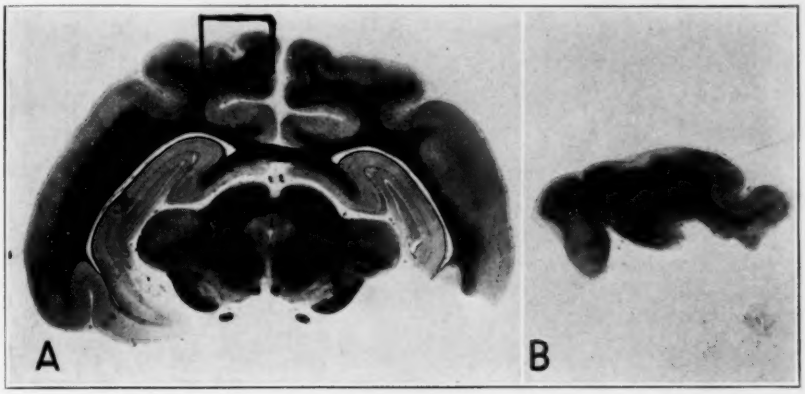

Fig. 2.—Coronal sections through the parietal lobe (*A*) and one occipital pole (*B*) of cat 22. Weil modification of the Pal-Weigert stain. A stripe of cortical necrosis with loss of tissue is seen in the gyri lateralis and suprasylvius posterior and underlying the sulcus lateralis (*A*). Patchy foci and stripelike necrosis can also be seen in the cortex of the occipital pole (*B*). Except for these areas, the remainder of the cortex shows no gross destruction.

fragmenting, and others had completely disappeared. Apparently, by the end of a week most of the cells had either regained morphologic normality or showed evidence of irreparable injury. The only change of significance in the basal nuclei was the presence of a large number of cells in which the cytoplasm took the stain more deeply than usual. These may represent cells which were recovering. In some folia of the cerebellum there were a few shrunken cells, but in others the Purkinje cells looked almost normal.

The other animals in this group showed similar, but generally more marked, changes in the brain. The areas of the cortex involved in frank necrosis were small and limited to the supramarginal and lateral gyri anteriorly (motor cortex) and to the posterior lateral and splenial gyri (visual cortex). No portion of

the cortex, however, failed to show some evidence of injury, although the orbital, temporal and olfactory gyri showed the least damage. The large and small pyramidal cells were always the most injured, which accounts for the diffuse degeneration noted in the motor and premotor areas of the cortex. The Purkinje cells of the cerebellum showed some evidence of degeneration. The basal nuclei

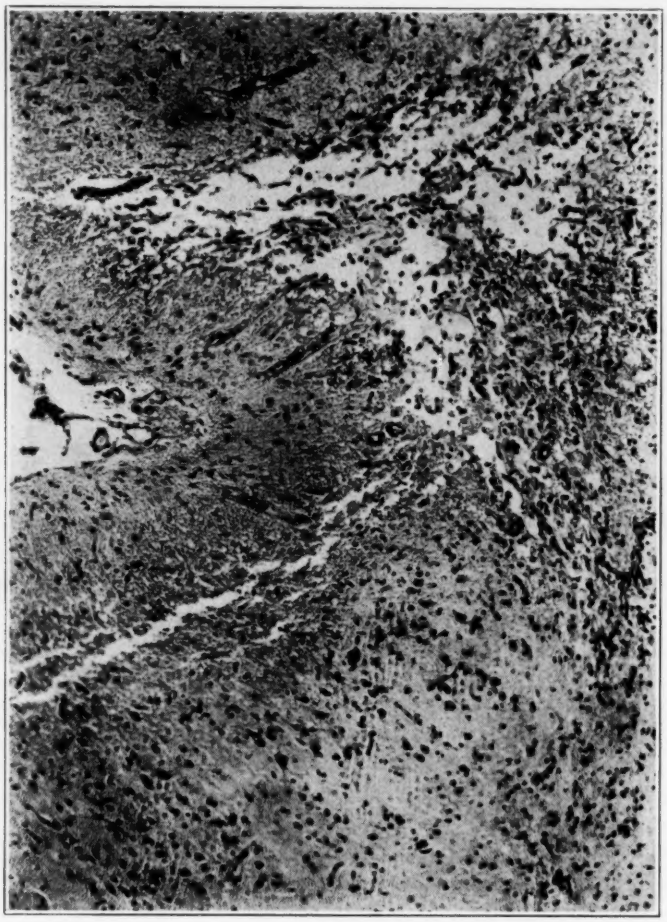

Fig. 3.—High power enlargement of the area indicated by the square in figure 2 *A* (cat 22). Cresyl violet stain. The softening and fragmentation of the cortex occupy all the deeper laminas toward the top of the illustration, but in the lower half a thin zone of necrosis can be seen which involves principally lamina III. Large numbers of gitter cells are scattered in the debris. There is no evidence of repair, but the capillaries are increased in the neighborhood of the softening.

showed patchy loss of cells and many scattered degenerated ganglion cells. The lateral geniculate nucleus was most affected, the caudate nucleus least. No frank necrosis was observed in the basal nuclei.

GROUP 3.—Circulatory arrest: Six minutes and seven seconds to seven minutes and five seconds.

The animals in this group exhibited signs of cortical injury which were pronounced immediately after operation. There was an initial period of coma, followed by bouts of wild hyperactivity. Tonic and clonic convulsions were exhibited by several animals. There was gradual improvement during the first week. Ability to stand, and then to walk, returned. All of the cats were blind. Cat 25, which survived six weeks, showed some return of vision. The distribution of the pathologic changes in this group was similar to that in group 2, but there was a definite increase in the extent of the injury.

The pathologic descriptions of the brains of 2 cats in this group follow. Cat 33 was killed on the second day because of infection of a wound; consequently the

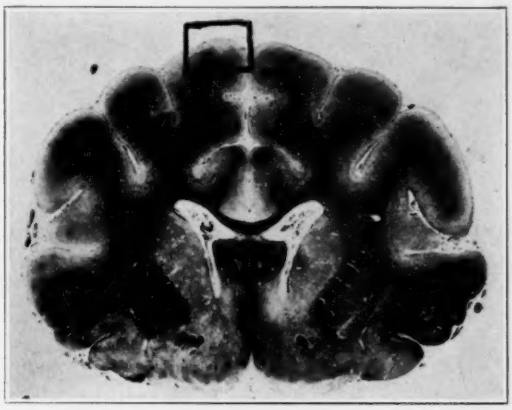

Fig. 4.—Coronal section through the frontal lobes of cat 33. Weil modification of the Pal-Weigert stain. A small area of cortical necrosis and fragmentation is bounded by the square. It is confined typically to the lateral gyrus.

pathologic changes were more acute than those in the other animal. On gross inspection a thin stripe of cortical disintegration could be seen in the gyrus lateralis (fig. 4). With magnification (fig. 5) a zone of coagulation necrosis and dissolution could be seen involving mainly lamina II and extending into lamina III. Outside the zone of necrosis the capillaries had proliferated, and their endothelium was swollen. In cortical areas 5, 6 and 7 almost no ganglion cells were seen in laminas III, IV and V. The few remaining cells were shrunken and amorphous. In the rest of the cortex there were marked disturbances of the cytoarchitecture and patchy foci of loss of cells and cell necrosis with widespread degeneration of ganglion cells. The lamellar decimation of the nerve cells with preservation of the glia was striking. There was no increase in the number of glia cells, and gitter cells were not present. In the temporal, olfactory and orbital gyri the cytoarchitecture was disarranged, and there were large numbers of shrunken and shriveled cells, many swollen and diffusely chromatolyzed forms and diffuse and focal loss of cells. Again, laminas III and IV were more severely injured than the other layers of the cortex.

The basal nuclei showed much milder alterations. There were a heavy, diffuse scattering of greatly swollen nerve cells with finely granular, glassy cytoplasm and a large number of disintegrating cells. The caudate nucleus was the least effected, the lateral geniculate nucleus the most. The Purkinje cells of the cerebellum were pale and swollen. The chromatin was collected under the perikaryon,

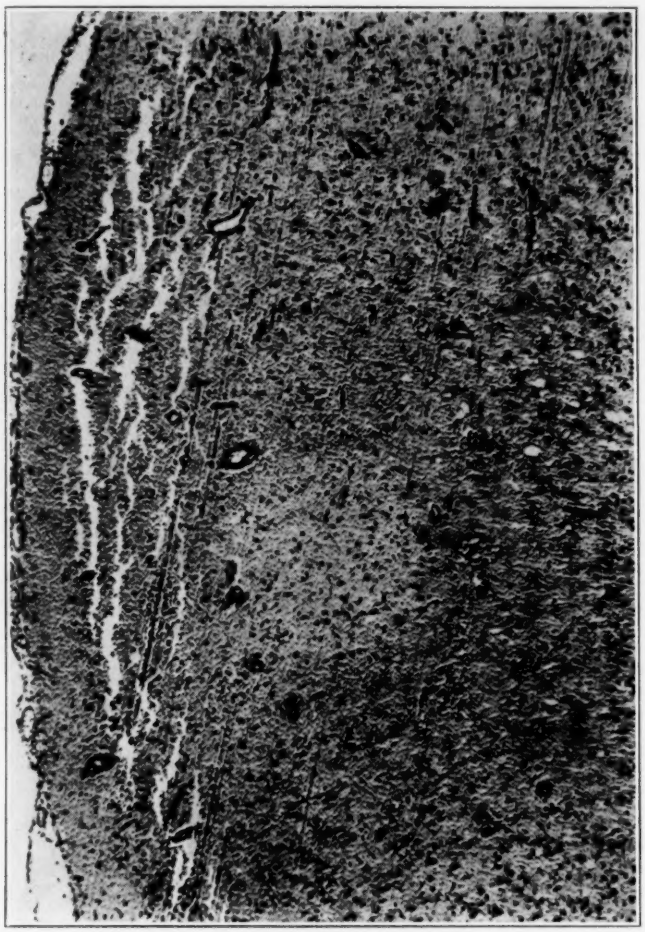

Fig. 5.—Enlargement of the segment designated by the square in figure 4 (cat 33). Cresyl violet stain. A zone of softening, with early fragmentation of lamina II, is shown. Practically no ganglion cells remain in laminas III or IV, but they may still be seen in laminas V and VI at the right of the illustration. A round area of marked paling may be seen mainly occupying laminas III and IV. The vertical streaks are artefacts, due to wrinkling of the section.

and the central portion of the cytoplasm was opaque. A few folia had a number of shrunken forms. The brain stem, except for sparse scattering of degenerated cells, was normal.

Cat 25 was killed at the end of six weeks. At this time all ordinary motor functions were normal except that peculiar widespread postures of the hindlegs were spontaneously assumed. There was still a marked degree of visual impairment. The animal was stupid, inactive and apathetic, although it would not tolerate being placed in water and escaped from noxious odors.

Gross inspection of sections stained with the Pal-Weigert technic showed obvious atrophy of the gyri and widening of the sulci (fig. 6). The other striking change was the extensive stripe of cortical disintegration with loss of tissue substance. This stripe of disintegration was most marked in the gyri suprasplenialis and lateralis. It was present in the gyrus suprasylvius medianus and

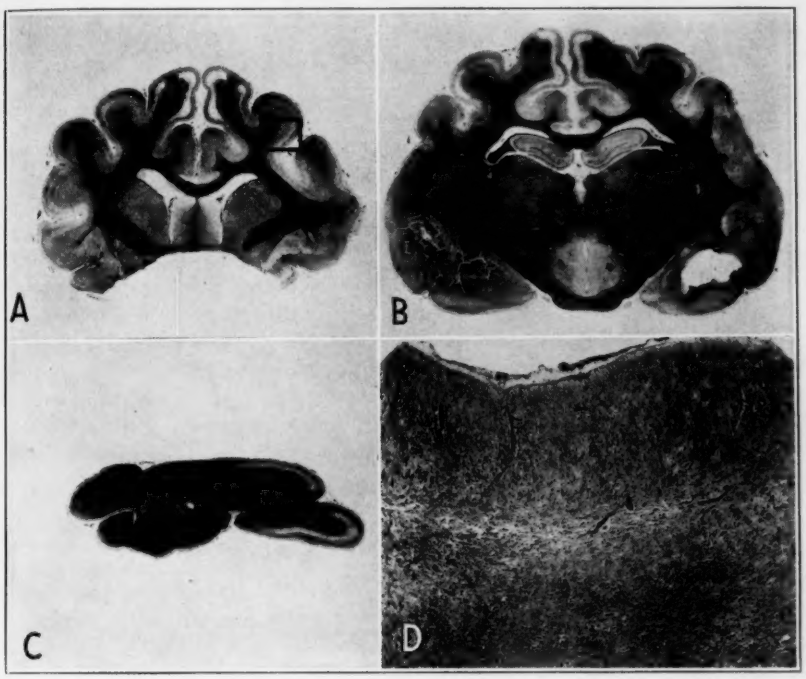

Fig. 6.—*A, B* and *C,* coronal sections through the frontal, parietal and one occipital lobe, respectively, of cat 25. Weil modification of the Pal-Weigert stain. Destruction of the cortex of the gyri lateralis and suprasplenialis and of the cortex of the occipital pole is obvious. The gyri suprasylvius medianus and ectosylvius medianus show thin lamellar stripes of necrosis. *D,* enlargement of the segment outlined in *A*. The lamellar necrosis involving laminas III and IV is apparent.

to a slight degree in the gyrus ectosylvius medianus. The areas corresponded to the anterior limbic, the preparietal and a portion of the postcentral cortex, comprising for the most part the area of large pyramidal cells. There was no massive dissolution in the olfactory, temporal and orbital gyri, which comprise the agranular and granular cortex. On the other hand, in the occipital pole, containing the paraoccipital, preoccipital and occipital cortical areas (areas 17, 18 and 19), the cortex was grossly destroyed. Laminas I and II were for the

most part intact so far as continuity of tissue was concerned. The extent of destruction in other laminas varied considerably. In some sections laminas III, IV, V and VI were entirely absent, laminas III and IV showing the greatest damage in nearly every section.

Under high magnification great loss of tissue substance was evident. The remaining material in these areas was composed of debris, many fat-laden gitter cells and inflammatory and swollen glia cells. There was marked capillary and endothelial proliferation, with the formation of a fibroblastic and mesodermal reticulum. The coarse mesodermal-glial meshwork enclosed multiple small cysts. In the portions of the cortex where gross dissolution of tissue had not taken place the lamellar cytoarchitecture of the cortex was disrupted, and the cortex looked "wind-blown." This effect was produced by marked loss of cells and by areas which were completely lacking in ganglion cells. There were, in addition, focal areas of shriveled and fragmented nerve cells. No part of the cortex was entirely normal, and the majority of the ganglion cells in all sections showed degenerative alterations.

The subcortex showed numerous areas of sponginess and rarefaction, but no definite softening. The glia was increased, and there were numerous glial nodules. The lateral geniculate nucleus showed more marked changes than any other of the basal nuclei. There was diffuse and focal loss of cells, and many remaining nerve cells showed degenerative changes. Throughout the thalamic, hypothalamic and pallidal nuclei there were foci of cell loss and many scattered degenerated cells. There was a slight, but definite, increase of both glia nuclei and capillaries. Perivascular infiltration was seen. The caudate nucleus was the least affected, showing only questionable diminution in the number of cells and thin scattering of degenerated cells. In the cerebellum, a large number of Purkinje cells were degenerated, and in some folia many of them had disappeared. The site of the obliterated cells was occupied by accumulations of glia cells. The ganglion cells of the cerebellar cortex were normal.

GROUP 4.—Circulatory arrest: Seven minutes and thirty-six seconds to seven minutes and forty-five seconds.

This group comprises animals that withstood the longest period of cerebral circulatory arrest compatible with chronic survival. Cat 31 was subjected to circulatory arrest for seven minutes and thirty-six seconds, and died on the fifth day. Shortly before death the animal lay on its side, with the forelegs rigidly extended close to the body and the forepaws acutely flexed and spastic. The hindlegs were stiffly extended. The back, neck and extremities were spastic, and there were continuous gross, rhythmic tremors of the head and extremities. These were punctuated by short, jerking convulsions of the head and forelegs. The animal appeared completely blind and did not react to a strong light flashed into its eyes. It did not respond to pinching the tail except by making feeble stepping movements with its hindlegs. It required feeding with a tube, owing to the extreme spasticity of its jaws.

Macroscopically, sections stained with the Pal-Weigert method showed widespread spongy loss of tissue, involving almost the entire cortex (fig. 7). The lateral

and suprasplenial gyri and the posterior lateral and posterior splenial gyri (occipital lobe) appeared to have suffered the most intense destruction. Even the cortex of the olfactory and pyriform and the posterior sylvian and ectosylvian gyri were largely destroyed.

Cell stains showed that these areas of the cortex were the site of massive coagulation and liquefaction necrosis. In some areas all the layers of the cerebral cortex were equally destroyed; in others, one or several laminas only were involved. The supramarginal layer was mainly preserved, and laminas III and IV were uniformly the most affected. In the areas of softening even the vessels were destroyed and their debris was fused with the mass of softened cortical tissue. The necrotic material was packed with gitter cells possessing abundant, foamy cytoplasm. Stains for fat (scarlet red) showed fat not only filling the gitter cells but lying free in large amounts. In the areas adjacent to the necrosis there was marked proliferation of capillaries, with swelling and reduplication of the endothelium. There were many perivascular collections of inflammatory cells, and the zones adjacent to the softenings were diffusely infiltrated with the lymphocytes and with large swollen gemästete cells. Many transitional stages between relatively intact tissue and the disintegrated areas with great loss of substance were seen. The process seemed to begin with an area of coagulation necrosis, in which the

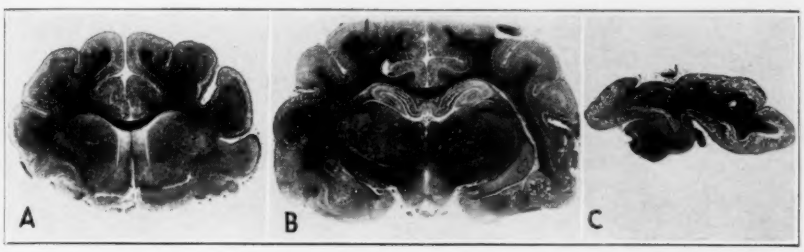

Fig. 7.—*A*, *B* and *C*, coronal sections through the frontal, parietal and one occipital lobe, respectively, of cat 31. Weil modification of the Pal-Weigert stain. The spongy necrosis and dissolution of the entire neocortex are evident. The cortex of the occipital lobe shows the most severe disintegration.

ground substance and the cellular content lost definition and fused into an amorphous caseous mass. This coagulated tissue then started to dissolve in the immediate vicinity of a vessel, forming a spongy, vacuolated area. This extended and coalesced with similar areas around neighboring vessels until large areas of such dissolution existed. Fragmentation and disintegration then occurred. Even in the less severely injured portions of the cortex no normal nerve cells could be seen. The basal nuclei showed no foci of softening, but there were numerous areas in which the ground substance was frayed and spongy. There was widespread decimation of cells, both diffuse and focal, and most of the remaining ganglion cells showed severe degenerative changes. Most of them were irregular, due to shrinking or swelling, and their cytoplasm was darkly stained. Large numbers were pyknotic, and a few were ballooned and possessed diffusely chromatolyzed cytoplasm. Almost no normal nerve cells could be seen. The capillaries were moderately increased in number. The lateral geniculate body was most severely degenerated, then, in order, the hypothalamic, the thalamic and the caudate nuclei.

Almost all the Purkinje cells in the cerebellum had disappeared, leaving only vacant holes to mark their sites (fig. 8). Throughout the brain stem there were many scattered degenerated cells. Most of the nuclei of the brain stem were normal.

The pulmonary artery of cat 8 was clamped for five minutes. This was one of the early experiments, in which the retina was not watched to note the time

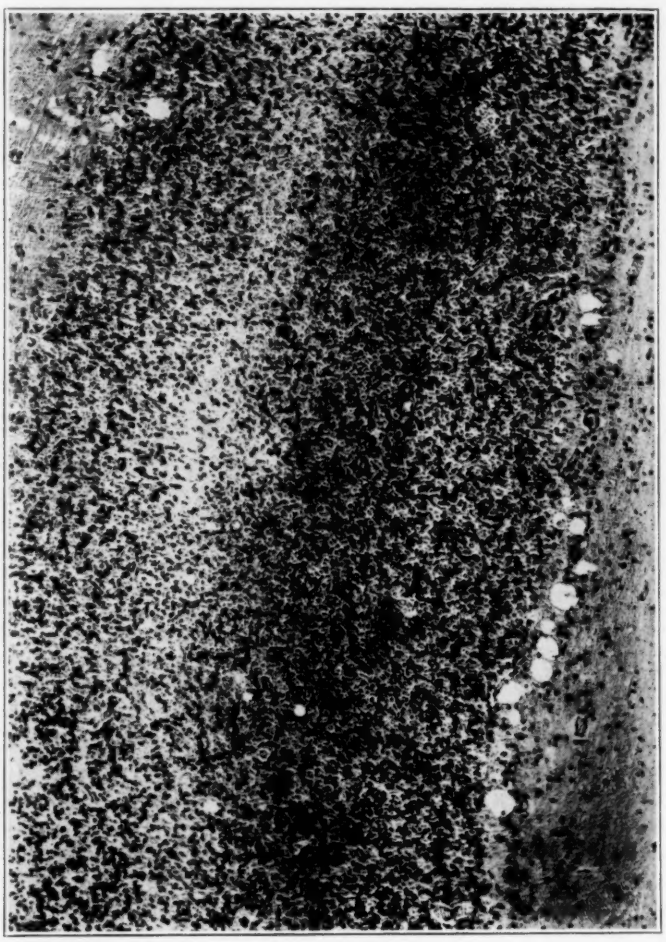

Fig. 8.—High power view of a cerebellar folium of cat 31. Cresyl violet stain. The Purkinje cells have disappeared, and their former sites are marked by the empty holes in the plexiform layer.

when the circulation reappeared in the retinal vessels. Owing to delayed measures of resuscitation on release of the pulmonary artery, it is probable that the flow of blood to the brain was not restored for an additional two or three minutes. The animal was killed at the end of six weeks, at which time it was blind and profoundly demented. Motor weakness and spasticity were present, and defects in placing and hopping reactions were demonstrable. The cat was unable to climb

or balance and could not right itself in the air when dropped. It was able to lap milk but had difficulty in swallowing solid food. Attacks of "sham rage" were sometimes exhibited. The brain of this cat showed the most extensive pathologic changes in the series.

Macroscopically, the cortex appeared to be almost completely disintegrated (fig. 9). The site normally occupied by the cortex was represented by a stripe of dissolution, containing almost no tissue. This zone of disintegration was limited superficially by the meninges and a thin remnant of the outer cortical layers, and internally by the medullary substance. The loss of cortical substance involved all lobes, but the orbital and olfactory gyri were affected less than the others. The gyri were shrunken and atrophic, and the sulci were widened and deepened.

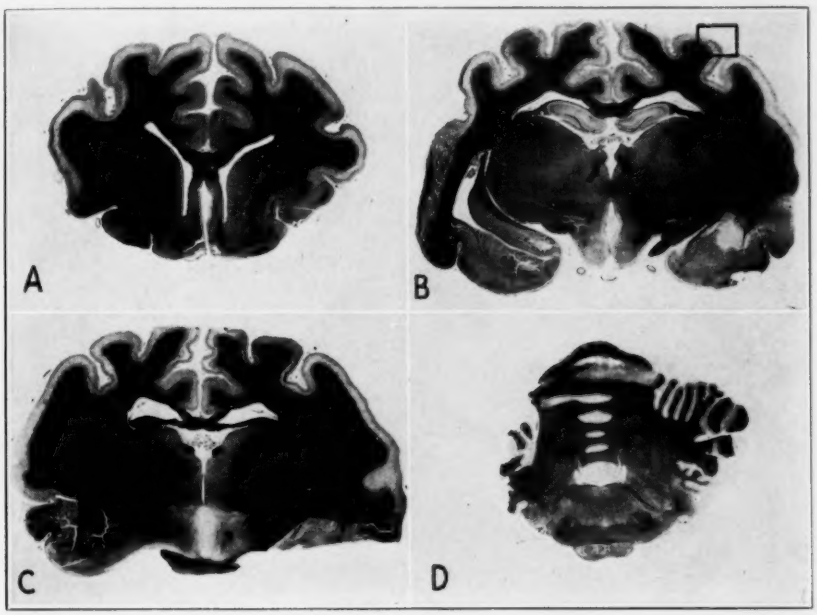

Fig. 9.—*A*, *B* and *C*, coronal sections through three levels of the cerebrum of cat 8. The cerebral cortex is almost entirely destroyed. The subpial layer is still preserved, but there is uniform dissolution of the deeper cortical laminas. The gyri are shrunken and the sulci deepened. The cracks in the lower part of the sections are artefacts. *D*, section through the cerebellum. The folia are slightly atrophic, and there is paling of the myelin in the pyramids. Weil modification of the Pal-Weigert stain.

The myelin of the centrum ovale and the internal capsule showed focal and diffuse areas of paling.

The sections stained with cresyl violet showed that the cortex had suffered extensive necrosis, softening and disintegration (fig. 10 *A*). The supramarginal layer, lamina I and parts of lamina II were relatively intact, although spongy and rarefied in some areas. A few shriveled and fragmented ganglion cells were still seen in these laminas. On the other hand, laminas III, V and VI were completely disintegrated. There were cuffs of inflammatory cells about many

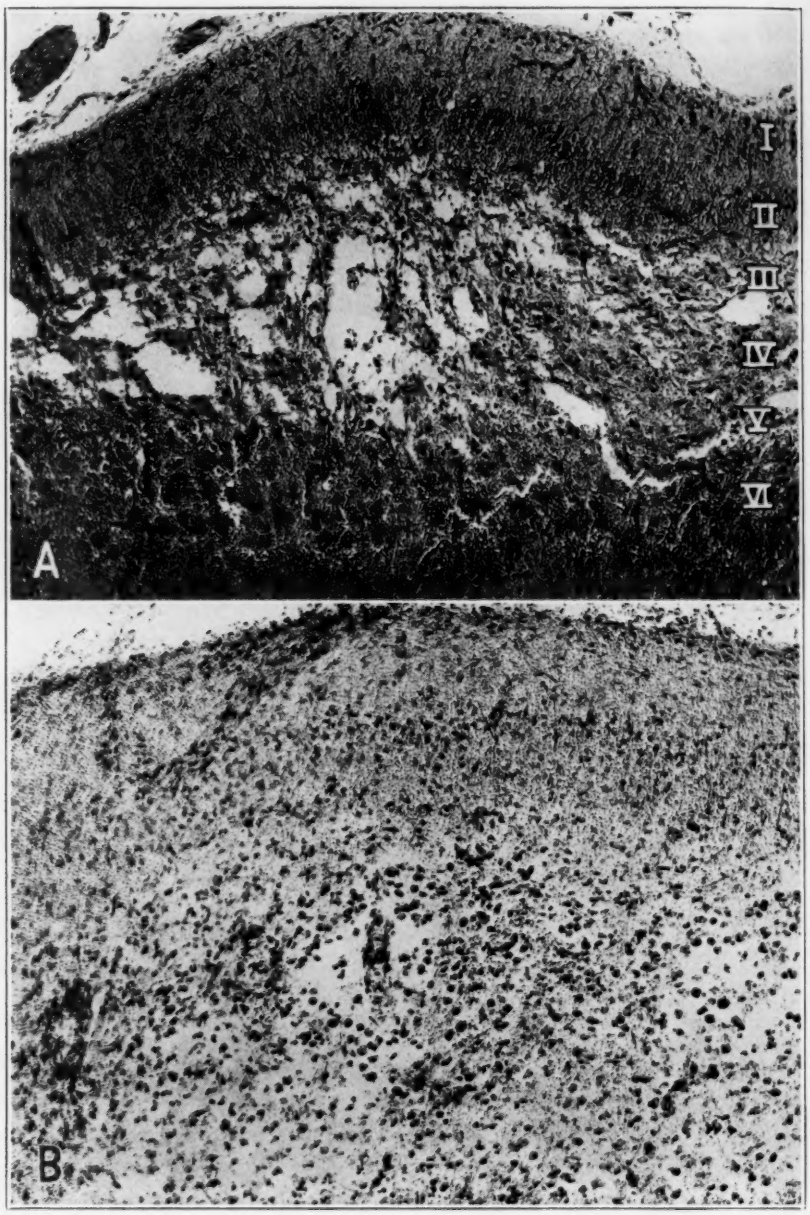

Fig. 10.—*A*, greater magnification of the area designated by the square in figure 9 *B* (cat 8). Pal-Weigert stain. The disruption and breakdown of the cortex are well shown. Laminas III, IV and V are the most severely damaged and are represented only by tissue debris and reparative processes. *B*, section of the cortex (cat 8); scarlet red stain. Numerous fat-laden gitter cells are apparent.

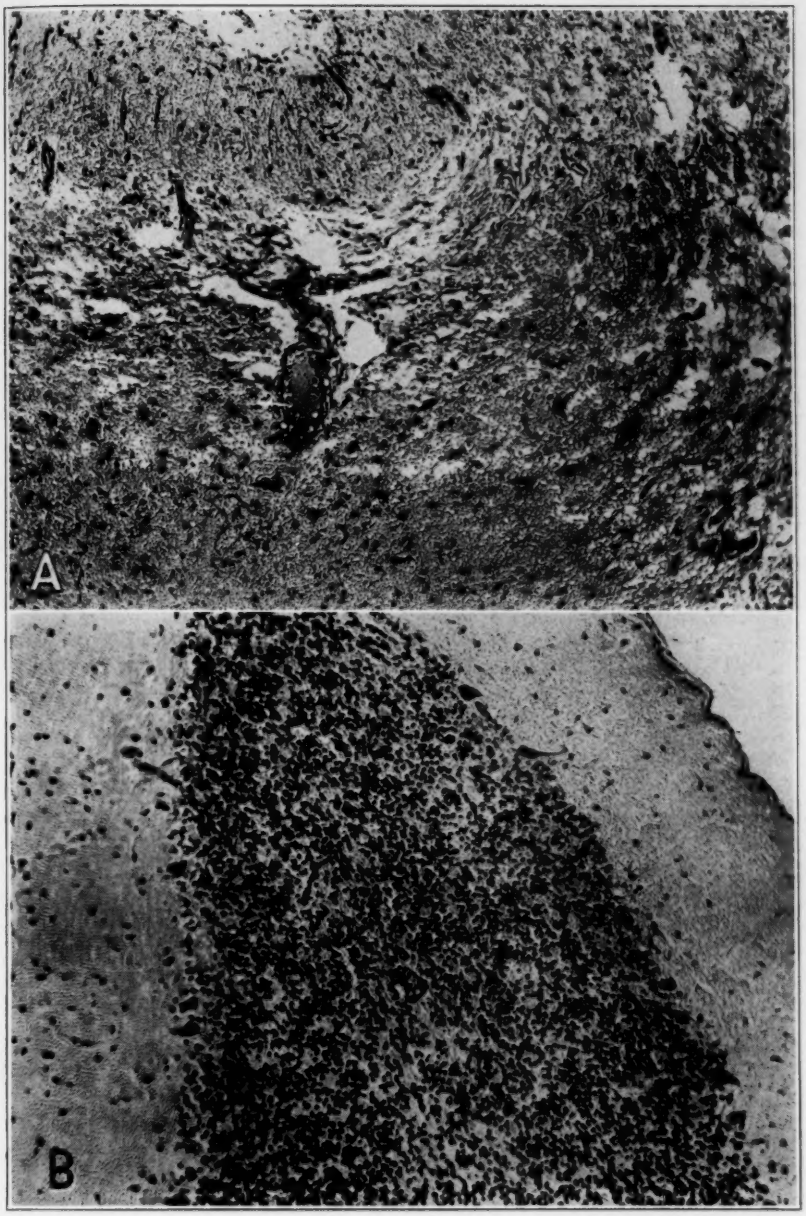

Fig. 11.—*A*, section of the cortex of cat 8. Masson's trichrome stain. The small vessels bound together by a fibroreticulum can be seen at the right. Fibroblasts proliferate from the walls of the large vessel in the center of the picture. *B*, section through a cerebellar folium of cat 8. Cresyl violet stain. The great loss of Purkinje cells is apparent. The few remaining Purkinje cells are shrunken and pyknotic.

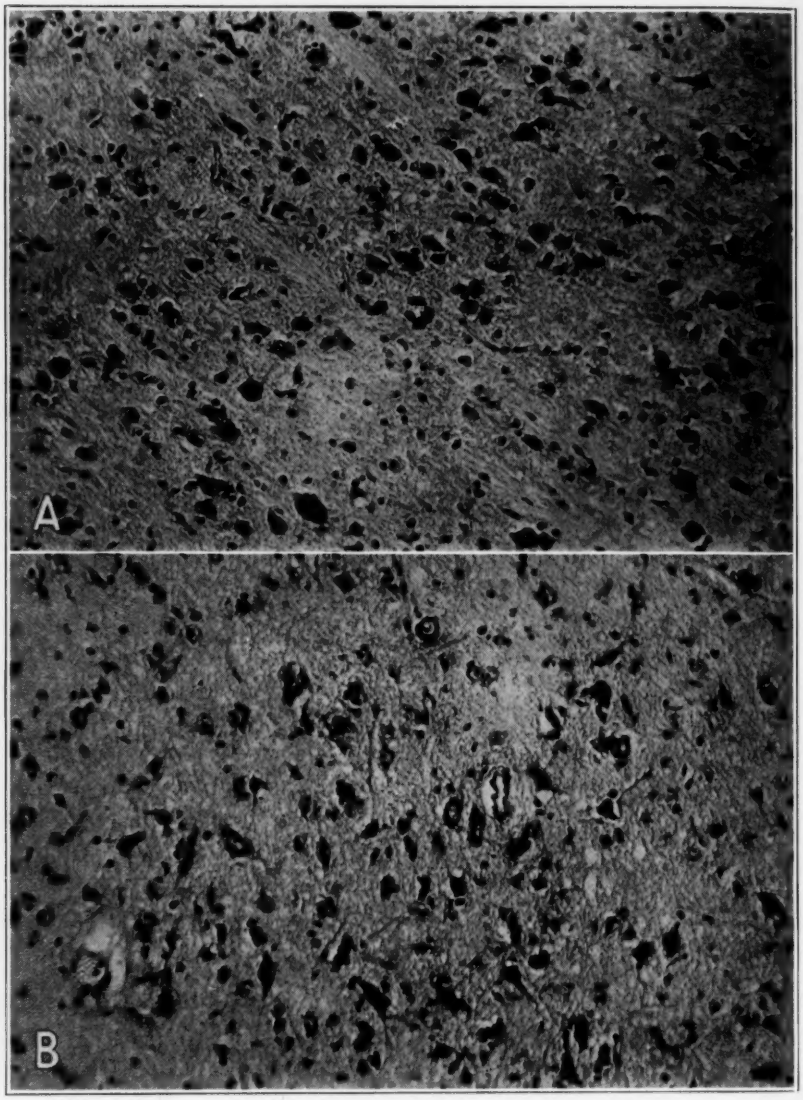

Fig. 12.—*A*, section through the lateral geniculate nucleus of cat 8. Loss of cells can be seen. The remaining cells are shrunken and darkly stained. The ground substance is spongy and rarefied. *B*, section through the filiform nucleus of the hypothalamus of cat 8. The ganglion cells are shriveled and amorphously stained. The ground substance shows more pronounced spongy degeneration than in that pictured in *A*. Cresyl violet stain.

of the small arterioles, and these cells had infiltrated the tissue debris. Many capillary buds were present, and the vascular endothelium was swollen and proliferated. Stains for fat showed large numbers of fat-laden gitter cells in the necrotic areas (fig. 10 *B*). In places they appeared to have discharged into the subarachnoid space. The leptomeninges were thickened and infiltrated with small mononuclear cells.

All portions of the cortex were not affected in the same degree. In some gyri only laminas III and IV were disintegrated. Although the number of layers which were fragmented varied considerably, laminas III and IV seemed uniformly the most affected. In one or two places the area of necrosis extended a short distance into the medullary substance. Stains for connective tissue and glia fibers demonstrated the presence of early reparative processes. Young fibroblasts, which had sprouted into the debris from the capillary walls, could be seen, and a fine mesodermal reticulum had spread through the areas of tissue loss (fig. 11 *A*). Glia fibers from the supramarginal layer had grown into the disintegrated zones and intermingled with the mesodermal meshwork. The glial components, however, were scanty. The young vasculoglial-mesodermal scar enclosed small vacant spaces to form multiple cysts, looking somewhat like a coarse sponge. Efforts toward scar formation were seen only in those areas in which there had been frank dissolution of tissue. In other portions of the cortex where this had not occurred there was moderate glial proliferation.

There were numerous areas of sponginess and rarefaction in the subcortex. Occasional small focal areas of softening in the centrum ovale were occupied by debris and gitter cells. Perivascular infiltration was common, and in some areas the white matter was thinly and diffusely infiltrated with inflammatory cells. The glial activity was far greater here than in the cortex, and there were many focal accumulations of glial nuclei.

The Purkinje cells were markedly affected. In some folia only a few remained, and these were shrunken and amorphously stained (fig. 11 *B*). In other folia the normal complement of Purkinje cells was present, but many of them were shriveled and darkly stained. There was an increase in the number of glia nuclei in the plexiform layer. The small nerve cells of the cerebellar cortex were apparently normal, but the large ganglion cells showed varying degrees of degenerative change. There was a definite loss of cells in the dentate nucleus, and a number of shadow forms were seen. In the dentate nucleus glia cells had proliferated in cuffs around the nerve cells, giving an appearance much like that of capsule cells around posterior ganglion cells.

In the lateral geniculate nucleus, the anterior, medial, lateral and ventral thalamic and hypothalamic nuclei, the globus pallidus and the caudate nucleus there were patchy and diffuse loss of cells and many scattered degenerated and degenerating forms. Many focal perivascular infiltrations were seen. The greatest loss of cells, as well as the greatest number of degenerated, shrunken and pyknotic nerve cells (fig. 12 *A*), occurred in the lateral geniculate nucleus. The hypothalamic nuclei (fig. 12 *B*), the thalamic nuclei (fig. 13 *A*), the globus pallidus and the caudate nucleus (fig. 13 *B*) followed, in descending order of injury. Some glial proliferation and increase in capillarity were observed in all the basal nuclei. There were no areas of frank necrosis, but in a number of places the ground substance was frayed and spongy. Scattered degenerated ganglion cells occurred at all levels of the midbrain, pons and medulla, but for the most part the nuclei of the brain stem were normal. There were occasional inflammatory infiltrations in the brain stem.

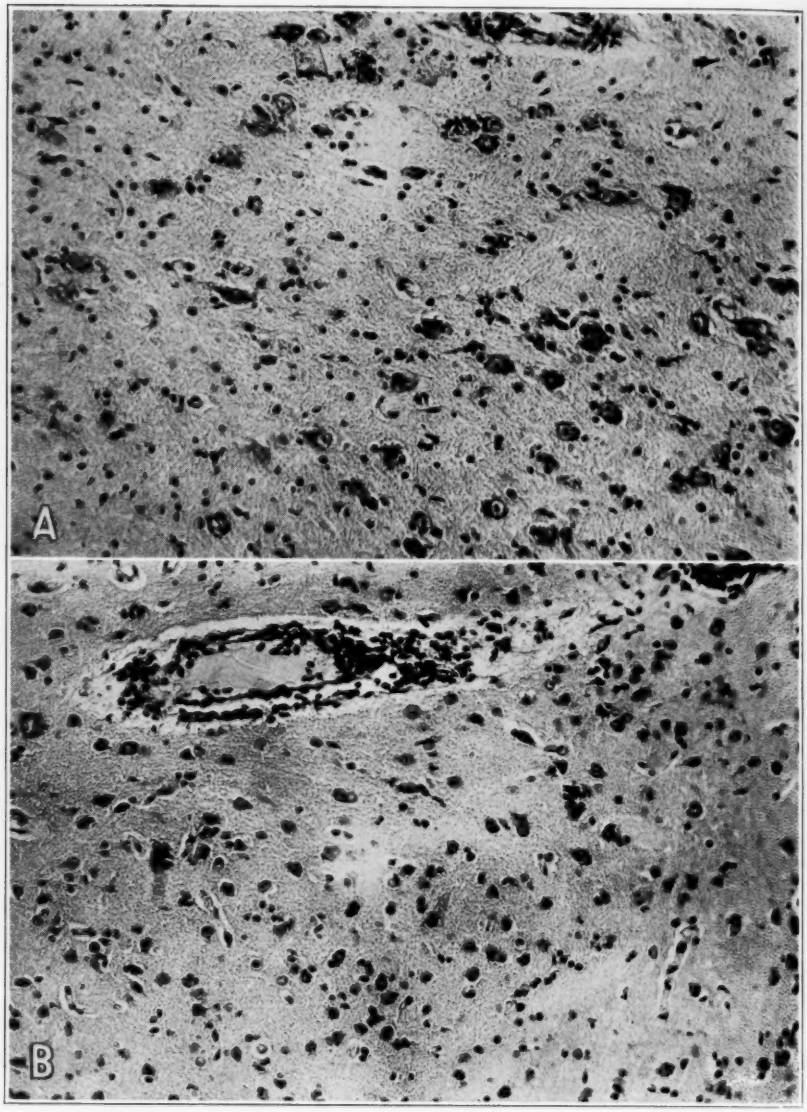

Fig. 13.—*A*, section through the lateral thalamic nucleus of cat 8. There is some loss of cells, but the remaining cells are fairly well preserved. Pale areas in the ground substance are seen at the upper part of the picture. *B*, section through the caudate nucleus of cat 8. There are scattered areas of cell loss. The ganglion cells are for the most part normal, although there are scattered degenerated cells. One of the common perivascular infiltrations is present in this section. Several areas of paling can be seen. Cresyl violet stain.

RELATION OF TIME OF CIRCULATORY ARREST TO PATHOLOGIC ALTERATIONS

No pathologic changes were observed in the brains of cats in which the circulation was arrested for two minutes. One animal subjected to three minutes and ten seconds of circulatory arrest showed permanent pathologic alterations in the cerebral cortex. Cortical areas of frank softening and tissue dissolution followed interruption of the circulation for as short a period as three minutes and twenty-five seconds.

With circulatory arrest for from three minutes and twenty-five seconds to approximately seven and a half minutes the pathologic changes became more extensive as the period of circulatory arrest increased. After cessation of cerebral blood flow for six minutes the cortical necrosis and dissolution became widespread. With periods longer than seven and a half minutes the injury to the brain was so profound that survival appeared to be impossible for more than a few hours. All cats subjected to periods of circulatory interruption longer than this died, probably before cortical softening could occur.

It is difficult to estimate the period of circulatory arrest necessary to produce changes in the basal nuclei because the alterations were less clearcut. However, it required approximately six or seven minutes of arrest of the blood flow to produce in the basal nuclei changes corresponding to those produced in the cerebral cortex by three to three and a half minutes of circulatory arrest. On the other hand, the Purkinje cells of the cerebellum were hardly less susceptible than the cortical nerve cells. Whenever the cortex was necrotic, the Purkinje cells were largely lost or degenerated. The cerebellum, however, was never subject to gross tissue softening. The brain stem, by comparison, appeared to be highly resistant to the effects of circulatory arrest. Even in the animals in which the cortex was largely destroyed, there was only a thin scattering of degenerated nerve cells in the nuclei of the brain stem. The spinal cord was uniformly normal in all the animals. In a few instances in which peripheral nerves and the sympathetic ganglia were examined no alterations were seen.

LOCALIZATION OF THE PATHOLOGIC PROCESS

The cerebral cortex obviously is the structure most vulnerable to anoxia, but within the cortex there are areas of greater and lesser susceptibility. Gross tissue dissolution, as well as the less serious alterations, occurred first in the suprasplenial and lateral gyri of the frontal cortex and in the posterior lateral and splenial gyri of the occipital cortex. These gyri correspond to cortical areas 5, 7, 18 and 19. With longer periods of circulatory arrest evidence of injury was observed in the fornicate and median ectosylvian gyri, cortical areas 3 and 6 and

frequently also area 29, the area retrolimbica posterior. The orbital, olfactory and temporal and a portion of the parietal cortex did not become grossly destroyed unless the period of circulatory arrest was long (cats 8 and 31, approximately seven and a half minutes). In terms of function, the motor and visual cortexes were the first to show injury and suffered the most extensive damage. The constancy of these specific vulnerabilities was such that if necrosis was not present in these areas it was never found in other parts of the cortex. Again, within the vulnerable cortex the laminas varied in susceptibility. In the most severely disintegrated cortical areas the structure of lamina I, and to a lesser extent of lamina II, was generally preserved. The deeper laminas, on the other hand, were destroyed, laminas III and IV bearing the greatest brunt of the destruction. In some sections a thin stripe of necrosis involving only laminas III and IV was present, sometimes extending the length of a gyrus. Whenever this occurred it affected almost exclusively these two laminas.

The Purkinje cells ranked next to the nerve cells of the cortex in vulnerability. The degeneration and loss of Purkinje cells resembled the degeneration and loss of cells in the least injured areas of the cortex. The degree and extent of the tissue changes varied among the basal nuclei. In all cases in which arrest of the circulation had been long enough to produce foci of cell loss and cellular degeneration in the basal nuclei, the lateral geniculate nucleus was always the most severely injured. In descending order of susceptibility were the hypothalamic nuclei, the several thalamic nuclei, the globus pallidus and the caudate nucleus.

The medullary substance of the cerebral hemispheres deserves brief mention. In the most severely injured animals there were a few small foci of softening in the centrum ovale. In the less seriously injured animals there were only scattered areas of sponginess and rarefaction. Numerous twisted and swollen myelin sheaths, however, were scattered diffusely through the subcortex. With short periods of circulatory arrest the myelin was normal.

NATURE OF PATHOLOGIC ALTERATIONS

Since, for the most part, some time intervened between the experiment and the examination of the brain, there was not much variety in the type of cellular degeneration. Shrunken, pyknotic and amorphously stained cells were most common. In a large number of cells the cytoplasm was coarsely granular, and the cell margins were frayed and crumbled, frequently leaving a naked vesicular nucleus, stripped of cytoplasm. Only in 2 animals were large swollen cells with opaque

glassy cytoplasm seen. These animals died at the end of thirty and fifty hours, respectively. The large encrusted cells that Gildea and Cobb [5] described were not encountered, but this may have been due to difference in staining technics.

Cortical destruction, wherever it occurred, consisted of ordinary ischemic softening involving a more or less wide sheet of cortex. There were the familiar processes of tissue coagulation followed by liquefaction, dissolution and fragmentation, and then phagocytosis by gitter cells. In the less seriously injured cortex the changes were somewhat similar to those encountered in chronic cerebrovascular disease. The difference lay in the slight glial reaction and in the presence of numerous foci of acute cortical devastation in which the ganglion cells were shriveled and fragmented. While gitter cells were not seen in these less injured areas, the microglia nuclei were increased in number and were longer and plumper than usual.

Frank tissue softening and liquefaction necrosis were observed as early as the end of the second day (fifty hours) following circulatory arrest of six minutes and thirty-five seconds. Great numbers of gitter cells containing fat were noted four and a half days after occlusion of seven minutes and thirty-six seconds. They were not present, however, in the areas of softening seen at the end of the second day. They presumably made their appearance between the second and the fourth day. Gitter cells laden with fat were still seen in the necrotic zones six weeks after the original injury.

The reparative processes had not begun in areas of tissue dissolution by the eighth day, and they were very young in animals examined at the end of six weeks. Indeed, the regressive changes still overshadowed the productive processes at this relatively late date. Attempts at scar formation were evident in the proliferation of many new capillaries. Fibroblasts sprouting from the walls of these masses of capillaries penetrated into the debris and formed a meshwork of reticulum and newly developed capillaries. The mesodermal reticulum intermingled with the scanty growth of glia fibers from the supramarginal layer to form a coarse meshwork enclosing multiple small cysts. In the areas of diffuse but not severe cortical damage the glia was only mildly increased at the end of six weeks and there was a moderate increase in the number of capillaries. The meninges were thickened in all the cats in which the cortex had undergone necrosis, and there was infiltration of inflammatory cells in the subarachnoid spaces. The amount of infiltration seemed to bear a relation to the number of fat-filled gitter cells that were discharged into the meningeal spaces.

COMMENT

Various estimates have been made in the past regarding the length of time that cortical cells can survive arrest of the circulation. Crile and Dolley [9] concluded that from six to seven minutes is the longest period that cortical cells can withstand anemia. The estimate of Gomez and Pike [3] was seven to eight minutes, that of Gildea and Cobb [5] was less than ten minutes and that of Heymans and Bouckaert [10] five minutes. In the experiments reported here definite changes were seen in the brain of 1 animal after circulatory arrest of three minutes and ten seconds, and marked damage in the cortex of another animal with circulatory arrest of three minutes and twenty-five seconds. The longer periods noted by earlier investigators, we believe, are due to the failure to produce complete arrest of the circulation by the experimental method employed.

The order in which various portions of the central nervous system are affected by circulatory arrest has been known for a long time. As early as 1858 Brown-Séquard [11] had demonstrated that the cerebrum, the medulla oblongata, the spinal cord and the peripheral nerves, in that order, were affected by temporary interruption of the blood supply. In 1909, Gomez and Pike [3] found that the small pyramidal cells of the cerebral cortex were the most sensitive to anemia, followed by the Purkinje cells of the cerebellum and the cells of the medulla oblongata, the cervical portion of the spinal cord and the spinal ganglia, in that order. In the experiments reported here the periods of circulatory arrest had to be short enough for compatibility with life. With these relatively short periods of circulatory arrest the spinal cord and medulla were uninjured. The cerebral cortex showed the greatest damage, followed by the Purkinje cells of the cerebellum and then the basal ganglia. MacArthur and Jones,[12] using in vitro methods of studying tissue respiration, found that the cerebrum and the cerebellum had approximately the same respiratory rate, which was the highest of the values for any nerve tissue studied. These structures were followed by the midbrain, the medulla oblongata, the corpus callosum, the spinal cord and the peripheral nerves, in order of decreasing metabolic rates.

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9. Crile, G., and Dolley, D. H.: On the Effect of Complete Anemia on the Central Nervous System in Dogs Resuscitated After Relative Death, J. Exper. Med. **10**:783, 1908.

10. Heymans, C., and Bouckaert, J. J.: Sur la survie et la réanimation des centres nerveux, Compt. rend. Soc. de biol. **119**:324, 1935.

11. Brown-Séquard, C. E.: Recherches expérimentales sur les propriétés physiologiques et les usages du sang rouge et du sang noir, J. de la physiol. de l'homme et des animaux **1**:119 and 364, 1858.

12. MacArthur, C. G., and Jones, O. C.: Some Factors Influencing the Respiration of Nervous Tissue, J. Biol. Chem. **32**:259, 1917.

As this order is similar to those already mentioned, it appears that the vulnerability of nerve cells to circulatory arrest is a function of their metabolic rates.

Laminas III and IV of the cerebral cortex appeared to be particularly susceptible to injury, both in the experiments described here and in those reported by Gildea and Cobb. It is probably impossible to determine directly the metabolic rates of the various laminas of the cortex. However, Dunning and Wolff [13] found that lamina IV of the cerebral cortex of the cat was the most vascular area of the cortex. Laminas II and III were almost as vascular, while laminas I, V and VI contained the smallest number of capillaries. Capillarity, of course, is not an index to metabolic activity, but the correlation between capillarity and injury following circulatory arrest is fairly striking.

Difference Between Circulatory Arrest and Lack of Oxygen.—During the period of complete interruption of blood flow to the brain, the nerve cells were deprived not only of oxygen but also of dextrose, and, in addition, the products of metabolic activity were not removed. These additional factors may have operated to produce or enhance some of the pathologic alterations. McGinty and Gesell [14] have shown, for example, that when the blood supply to the brain of dogs is abruptly cut off the lactic acid content of the brain increases rapidly at first, reaching a concentration approximately twice the normal value in the first four minutes. Thereafter the accumulation is less rapid, and a maximum of about two and a half times the normal value is reached in approximately ten minutes. This acidosis of the cerebral tissue probably contributes to proteolysis of the nerve cells.[15] Dextrose, which is important for normal neurometabolism, is withheld from the tissues during the period of circulatory interruption. Glickman and Gellhorn [16] have shown that convulsions induced by insulin are more severe and have a shorter latent period in the presence of oxygen deficiency. It is conceivable that the injury to nerve cells produced by deficiency of both dextrose and oxygen is more severe than that produced by the absence of either substance alone.

13. Dunning, H. S., and Wolff, H. G.: Relative Vascularity of Various Parts of Central and Peripheral Nervous System of Cat and Its Relation to Function, J. Comp. Neurol. **67**:433, 1937.

14. McGinty, D. A., and Gesell, R.: On the Chemical Regulation of Respiration: II. A Quantitative Study of the Accumulation of Lactic Acid in the Isolated Brain During Anaerobic Conditions and the Role of Lactic Acid as a Continuous Regulator of Respiration, Am. J. Physiol. **75**:70, 1925.

15. Rosenbohm, A.: Die Spaltungsprodukte des Glutathions im lebenden Gewebe und die Beziehung des Glutathions zum proteolytischen Abbau bei der Ausbreitung von Krebsgeschwülsten, Biochem. Ztschr. **289**:279, 1937.

16. Glickman, N., and Gellhorn, E.: Effect of Oxygen Deficiency on the Sensitivity of Rats to Insulin, Am. J. Physiol. **121**:358, 1938.

It has been difficult to produce structural changes in the cerebrum by exposing animals to atmospheres deficient in oxygen. Ford [17] was unable to discover any pathologic changes in the brains of kittens exposed to a mixture of nitrogen and 5.5 to 6 per cent oxygen for as long as twelve hours. Similarly, van Bogaert, Dallemagne and Wegria [18] could not produce pathologic changes in the nervous system of monkeys exposed to prolonged and severe lack of oxygen. The lack of oxygen was produced by sodium nitrite, carbon monoxide and a mixture of nitrogen and 6 per cent oxygen. Yant and his associates,[19] on the other hand, produced pathologic changes in the brains of dogs by asphyxiation with carbon monoxide. The animals were subjected to atmospheres containing 0.13 to 0.18 per cent of carbon monoxide for periods ranging from thirteen to nineteen hours. At the end of these periods the animals, which were then in deep coma, were allowed to recover. They were killed at intervals of sixteen to one hundred and sixty-five days. The neuropathologic changes consisted of focal areas of cortical disintegration, diffuse degeneration of the cortical ganglion cells, softening and cyst formation in the medullary substance, endothelial and capillary proliferation and marked neuroglial activity.

Correlation Between Experimental and Clinical Lesions.—It is now fairly well established that the action of nitrogen monoxide as an anesthetic is dependent on some degree of anoxemia, in addition to whatever specific narcotic action the gas may possess. Brown, Lucas and Henderson,[20] in a careful experimental study on animals, found that "surgical anesthesia cannot be produced with oxygen-nitrous oxide mixtures under pressure up to two atmospheres, if the partial pressure of oxygen is equal to that of the atmosphere, i. e. 156 mm." The deaths, dementias and permanent neurologic sequelae that have followed the use of this anesthetic are presumably due to cerebral asphyxia.

Courville [21] studied the brains of a number of patients who died after anesthesia induced with nitrogen monoxide, but who survived the opera-

17. Ford, F. R.: An Experimental Investigation into the Effects of Asphyxia on the Brain, Bull. Johns Hopkins Hosp. **42**:70, 1928.

18. van Bogaert, L.; Dallemagne, M. J., and Wegria, R.: Recherches sur le besoin d'oxygène chronique et aigu chez Macacus rhesus; absence de lésions expérimentales des centres nerveux après intoxication par l'oxyde de carbone, le nitrite de soude et l'appauvrissement de l'air en oxygène, Arch. internat. de méd. expér. **13**:335, 1938.

19. Yant, W. P.; Chornyak, J.; Schrenk, H. H.; Patty, F. A., and Sayers, R. R.: Studies in Asphyxia, Public Health Bulletin 211, United States Treasury Department, Public Health Service, 1934.

20. Brown, W. E.; Lucas, G. H. W., and Henderson, V. E.: The Anesthetic Value of Nitrous Oxide Under Pressure, J. Pharmacol. & Exper. Therap. **31**:269, 1927.

21. Courville, C. B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129, 1927.

tions for from several hours to several months. The pathologic changes consisted of focal areas of necrosis, stripelike zonal or laminar necrosis and softening of the cortex, diffuse degeneration of the cortical ganglion cells or diffuse cortical disintegration. Corresponding alterations occurred in the lenticular nucleus. The Purkinje cells of the cerebellum were frequently injured, while the nerve cells of the brain stem and spinal cord were unaltered. O'Brien and Steegmann [22] have also given an excellent description of the brain of a patient who died sixteen months after nitrogen monoxide anesthesia. They stated that "the third and part of the fourth cortical layers are in general the most selectively damaged, and present a pseudolaminar degeneration of a striking character." In general, the other changes are similar to those described by Courville. The means by which they were produced seem to be a serious degree of anoxia maintained for a relatively long period.[23] Gebauer and Coleman [24] have reported the pathologic changes in the brain of a patient seven days after cyclopropane anesthesia. There was irregular degeneration of the cortex, with the greatest cell defects apparent in laminas III, IV and V. Cellular degeneration was also present in the globus pallidus. There were no morphologic changes in the other parts of the brain. Tissue anoxia was thought to be the cause of these changes. Wilson and Winkelman [25] reported the case of a patient dying seventeen days after carbon monoxide asphyxiation, with a lesion confined to the third and fourth laminas of the cortex. However, they stated that "involvement of the globus pallidus is probably the commonest of all the pathologic changes that result from carbon monoxide poisoning."

In all essential respects, the pathologic changes seen in the nervous systems of these patients after carbon monoxide asphyxiation and accidents resulting from anesthesia are the same as those reported here in the brains of cats following experimental interruption of the circulation. The only striking dissimilarity is the frequent involvement of the lenticular nucleus in the human brains. Abbott and Courville [26] emphasized that "necrosis of the lenticular nucleus, particularly the globus pallidus, is an almost invariable finding" in human material. There appear to be several possible explanations for the discrepancy between

22. O'Brien, J. D., and Steegmann, A. T.: Severe Degeneration of the Brain Following Nitrous Oxide-Oxygen Anesthesia, Anesth. & Analg. **17**:101, 1938.

23. Courville, C. B.: The Pathogenesis of Necrosis of the Cerebral Gray Matter Following Nitrous Oxide Anesthesia, Ann. Surg. **107**:371, 1938.

24. Gebauer, P. W., and Coleman, F. P.: Postanesthetic Encephalopathy Following Cyclopropane, Ann. Surg. **107**:481, 1938.

25. Wilson, G., and Winkelman, N. W.: An Unusual Cortical Change in Carbon Monoxide Poisoning, Arch. Neurol. & Psychiat. **13**:191 (Feb.) 1925.

26. Abbott, C. N., and Courville, C. B.: Degeneration of the Globus Pallidus After Nitrous Oxide Anesthesia, Bull. Los Angeles Neurol. Soc. **3**:46, 1938.

the clinical and the experimental findings. Carbon monoxide and nitrogen monoxide may have a specific effect on the basal ganglia. Chornyak [27] has shown that the brains of different species of animals have different pathologic reactions to anoxia. This, again, may account for the discrepancy. Finally, lack of oxygen alone may produce an effect different from that produced by arrest of the circulation. The basal ganglia and the cortex may be equally injured by the lack of oxygen, whereas the combined lack of oxygen and dextrose, plus the effect of retained metabolites, may injure the cerebral cortex more than it does the basal ganglia in the same length of time. In our animals, in which all these factors operated, the cortex was more severely injured than the basal nuclei. In human beings, also, the cortex is always more involved than the basal ganglia in cerebrovascular disease.[28]

SUMMARY

1. Permanent pathologic lesions may occur in the cerebral cortex of the cat after complete arrest of the circulation for three minutes and ten seconds.

2. Frank necrosis and softening of the cortex have been observed after circulatory interruption for three minutes and twenty-five seconds.

3. Circulatory arrest for periods in the neighborhood of seven and a half minutes causes complete destruction and liquefaction necrosis of the cerebral cortex.

4. The motor and visual cortexes sustain the earliest and most profound damage. The olfactory, orbital and temporal regions of the cortex are the least susceptible.

5. Lamina I, and to a lesser extent lamina II, are the least vulnerable of the cortical layers, while laminas III and IV are the most vulnerable.

6. The Purkinje cells rank next to the nerve cells of the cerebral cortex in susceptibility.

7. The lateral geniculate nucleus is the most vulnerable of the basal nuclei in the cat, and it is followed, in order of susceptibility, by the hypothalamic nuclei, the thalamic nuclei, the globus pallidus and the caudate nucleus.

8. The brain stem and spinal cord are uninjured by periods of circulatory arrest compatible with continued survival of the animal.

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27. Chornyak, J.: The Structural Changes Produced in the Human Brain by Oxygen Deprivation and Their Pathogenesis, Thesis, University of Pennsylvania Graduate School, 1936.

28. Spielmeyer, W.: Vasomotorisch trophische Verhänderungen bei zerebraler Arteriosklerose, Monatschr. f. Psychiat. u. Neurol. **68**:605, 1928.

CERTAIN ASPECTS OF DEFECTS OF RECENT MEMORY OCCURRING IN PSYCHOSES OF THE SENIUM

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During a series of investigations into the thinking of patients suffering from psychoses occurring in the senium it was noted that there was an increased tendency to perseverate. This was particularly obvious when the patients were checked with regard to their capacity to deal with abstractions by having them reproduce designs. Since all the patients under investigation showed in varying degree involvement of their recent memory, tests were designed to clarify a possible relationship between the defects of recent memory and the increased tendency to perseverate. Later it was noted that these patients tended to show a progressive distortion of the memorized test material, and consequently a second study was set up to deal with this problem.

PROCEDURE

Since the patients showed considerable intellectual deterioration, the usual X-Y type of perseveration test, originated by Wynn Jones [1] and elaborated by others (Stephenson [1a] and Cameron [2]), could not be employed. Consequently, a set of paired figures was designed (fig. 1), of such nature that previous drawing of the first of each pair tended to disturb reproduction of the second of the pair, this disturbance being in the form of an appearance of the first of the pair in place of the second. Each figure was shown in turn to the patient, and he was asked to copy it immediately and then to reproduce it from memory.

To demonstrate the tendency to distort memorized material, the patient was asked to name two simple objects, e. g., a quarter and a match box, which had been presented on three immediately successive occasions and which had then been shown to him afterward, three times, and named by the investigator. At various intervals, usually two, five, nine minutes and so on after presentation, the patient was asked to state what he had been shown. The first investigation was carried out on 18 senile patients showing defects of recent memory and the second on 15 similar patients.

From the Department of Neurology and Psychiatry, Albany Medical College.

1. Jones, W., cited by Spearman, C.: The Abilities of Man, New York, The Macmillan Company, 1927, p. 295.

1a. Stephenson, W.: Studies in Experimental Psychiatry: Case of General Inertia, J. Ment. Sc. **77**:723-741, 1931.

2. Cameron, D. E., and Caunt, T. G. B.: Studies in Perseveration, J. Ment. Sc. **79**:735-745, 1933.

RESULTS

Of the 18 patients studied as to their tendency to perseverate, 9 showed the defect in marked degree, and it was possible to demonstrate that all these patients carried over the recollection of the first figure of a pair into the drawing of the second. In four cases this was apparent only when the patient was asked to draw the second member from memory (fig. 2 *A*). In five cases, however, the patient drew the first member of the pair when looking at the second member, after being asked to copy it (fig. 2 *B*); moreover, it was found in 2 instances that the patient did not copy the design but at once effected a compromise between it and something which he was accustomed to write, namely, his signature (fig. 3).

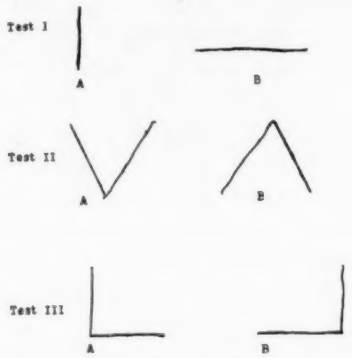

Fig. 1.—Drawings used in testing for perseveration.

Of the 15 patients studied as to their capacity to remember simple objects, 8 showed a marked tendency to distort these recollections (table 1 A and B). In all 8 instances this distortion occurred within fifteen minutes (table 2). A final form was rarely reached, the patient tending to continue to elaborate and distort his original recollections. It was noted, however, that occasionally after distortion occurred the patient returned to the original and correct recollection, though only transitorily.

COMMENT

Comparatively few data are available concerning the recent memory defect in the senium. Bleuler [3] stated in his discussion of the organic hypomnesias:

> The main disturbance is probably in the ability to recall, although the organic reduction of the associations hinders on the one hand the formation of parts through which the recollections can afterward be ekphorized; on the other hand, it impedes the use of these parts in the process of ekphoria.

3. Bleuler, E.: Textbook of Psychiatry, New York, The Macmillan Company, 1930, p. 99.

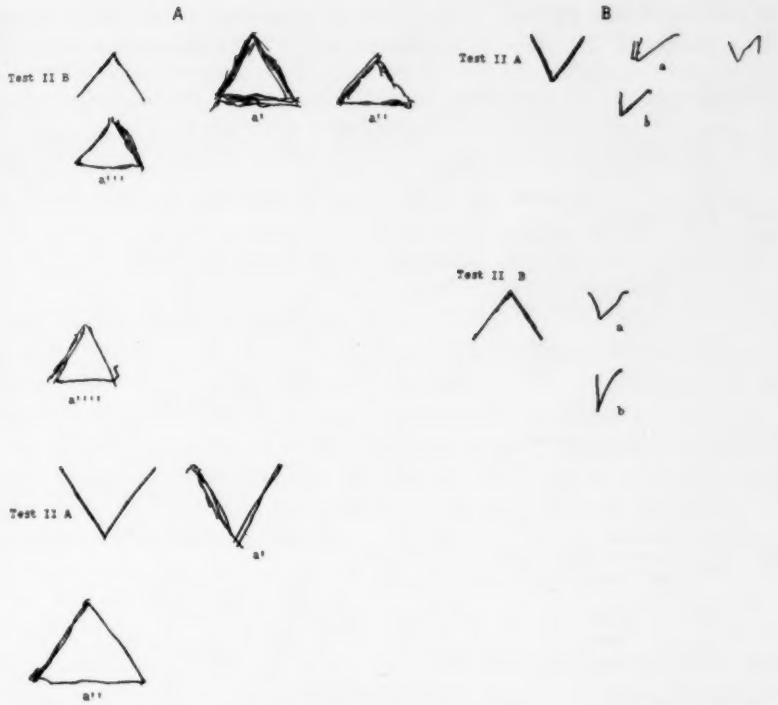

Fig. 2.—(*A*) In test II B, *a'* and *a''* are reproductions from copy; *a'''* is a reproduction from copy after it had been pointed out that there was no base line in the original drawing and the patient had admitted that there was only a green line. This shows definite perseveration. The drawing in *a''''* is a reproduction from memory. In test II A, *a'* is a reproduction from copy, and *a''*, a reproduction from memory.

(*B*) In test II A, *a* is a copy made on seeing the figure, and *b*, a reproduction from memory. In test II B, *a* is a copy on seeing the figure, and *b*, a reproduction from memory.

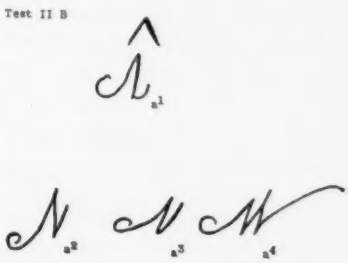

Fig. 3.—In test II B, $a,^1$ $a,^2$ a^3 and a^4 are reproductions from memory.

Curran and Schilder [4] stated that in their 1 patient with organic disease of the brain and in their 1 patient with Korsakoff's syndrome included in a group of 21 subjects a process which they described as that of

TABLE 1.—*Data on Senile Patients with Defects of Recent Memory Showing Tendency to Distortion of Recollection*

A (CASE 8)

Patient was shown a quarter and a key. He named them three times and was given their names three times.

Minutes	Question	Answer
2	What did I show you a few minutes ago?	Key with a ring on it
5	What did I show you a few minutes ago?	A watch and a key
9	What did I show you a few minutes ago?	A quarter and a 5 cent piece, and I think you had a nickel after that you showed me
14	What did I show you a few minutes ago?	A watch and chain, a quarter in your hand when you showed the watch. The watch had a short chain on it [the key had a small attachment]
20	What did I show you a few minutes ago?	Watch and chain
27	What did I show you a few minutes ago?	Watch and chain. You showed it to me twice, and it was that nickel that you showed me quite a few minutes after you showed me the watch and chain

B (CASE 7)

Patient was shown a spool of thread and a tooth brush. She named them three times and was told their names three times.

1	What did I show you a few minutes ago?	Tooth brush was in one hand and in the other a ring, I think
3	What did I show you a few minutes ago?	A ring on your hand
6	What did I show you a few minutes ago?	You showed me a ring on your hand
10	What did I show you a few minutes ago?	Well, there was a key you showed me. That's all.
15	What did I show you a few minutes ago?	You showed me—well, one was a ring
21	What did I show you a few minutes ago?	A ring, and there was nothing in the other hand

TABLE 2.—*Time Elapsing Between Presentation and Distortion of Objects*

Minutes	First Object	Second Object	Both Objects
1	Case 2; case 6 Case 7	Case 2; case 6	Case 2; case 6
2	Case 8		
3		Case 1; case 4 Case 7	Case 7
4			
5			
6	Case 1	Case 4	Case 1, case 4
7			
8			
9		Case 8	Case 8
10			
11			
12			
13			
14	Case 5	Case 5	Case 5
15	Case 3	Case 3	Case 3

"organizing a memory trace" was accelerated and exaggerated; i. e., the original reproduction became much more rapidly distorted than in the normal subjects.

4. Curran, F. J., and Schilder, P.: Experiments in Repetition and Recall, J. Genetic Psychol. **51**:163-187, 1937.

On the basis of the findings in the present study, it seems reasonable to state that both the greatly increased perseveration and the increased speed at which distortion and secondary elaboration take place are factors of considerable importance in the failure of recent memory in the senium. With regard to the first point, it may be said that in some instances perseveration is so severe that certain objects may be seen but not grasped for what they are. Under such circumstances these objects act rather to reproduce the image of what has gone immediately before. Consequently, it seems reasonable to suggest that, since they are never apperceived, they are not incorporated or registered as memories at all. The mechanism involved in the cases in which a second member of a pair was accurately copied but in which the first member of the pair or some other antecedent figure was substituted on attempted reproduction from memory is entirely different, but no definite explanation is offered at present.

With regard to the data obtained in the study of secondary elaboration, it can be stated that the activities which produce this are greatly accelerated and that this acceleration is a factor in the interference with recent memory.

Understanding can be carried a little further by consideration of what memory actually does for the person. First, it provides a means whereby data can be exactly reproduced, as in the keeping of appointments and the finding of references. This aspect of memory has been extensively studied by Ebbinghaus [5] and his intellectual descendants Second, memory provides a means whereby, after a series of learning trials, a final composite pattern of learned activity is brought out, rather than the reproduction of each learning trial. Third, memory permits the secondary elaboration of registered material. In part this is of obvious value to the organism in rendering what was unpleasant in the past less likely to appear and converting what was illogical into an acceptable form. Much of secondary elaboration, however, is still inexplicable on the basis of value, in spite of extensive work (Bartlett,[6] on "Legends," and other workers interested in testimony).

It is clear that these activities of memory—accurate reproduction, synthetic reproduction and reproduction after secondary elaboration—are in considerable measure mutually antagonistic. It is also clear that the aspects of memory which are lost in the senile persons are primarily accurate reproduction, and possibly synthetic reproduction. I therefore put forward as a suggestion that the great acceleration of secondary elaboration may be due to the loss of an inhibiting effect which the

5. Ebbinghaus, H.: Memory: A Contribution to Experimental Psychology, translated by H. A. Ruger and C. E. Bussenius, New York, Teachers College, Columbia University, 1913.

6. Bartlett, F. C.: Remembering, London, Cambridge University Press, 1932.

activities necessary for accurate and synthetic reproduction may exert on those necessary for secondary elaboration under normal conditions.

It is necessary to emphasize that I do not state that the failure of accurate reproduction is due to any of the activities, such as retroactive inhibition (Britt [7]) or hedonic tone (Sharp [8]), which operate during the phase of reproduction. These factors were not investigated. My data justify me in saying only that perseveration appears to interfere with registration; secondary elaboration, likewise, interferes with retention, and as a consequence accurate reproduction cannot be carried out.

SUMMARY

It was found that in patients suffering from the psychoses of the senium there are a greatly increased tendency to perseverate and a greatly accelerated tendency to secondary elaboration of memorized data. The first process, by interfering primarily with registration, and the second process, by interfering with retention, contribute materially to the impoverishment of recent memory in these patients.

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7. Britt, S. H.: Retroactive Inhibition: A Review of the Literature, Psychol. Bull. **32**:381-440, 1935.

8. Sharp, A. A.: Experimental Test of Freud's Doctrine of Relation of Hedonic Tone to Memory Revival, J. Exper. Psychol. **22**:395-418, 1938.

Case Reports

STATUS EPILEPTICUS AS A COMPLICATION OF METRAZOL CONVULSIVE THERAPY

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Because of the present extensive use of metrazol (pentamethylenetetrazol) in the treatment of the psychoses, and since it is clinically administered for cardiac and respiratory collapse, it was decided to report the serious complication of status epilepticus which occurred in the course of treating a psychotic patient.

REPORT OF A CASE

F. R., a white youth aged 18, was admitted to the Kankakee State Hospital on Jan. 5, 1935. The patient's maternal uncle, H. M., had been an inmate of this and other institutions for many years, with an illness diagnosed as paranoid dementia praecox. The patient's brother, D. R., had been confined here in 1929, and in various other sanatoriums; his illness was diagnosed as "mental deficiency with psychopathic tendencies"; he is at present in an institution for the criminally insane. Other than the aforementioned cases, the family history was negative for mental disease. No history of a convulsive tendency had been elicited either in the patient or in any other members of the family.

Prior to the onset of his illness the patient seemed to have developed in a normal fashion physically, intellectually and emotionally. Socially he always showed some shyness and bashfulness. His mental symptoms apparently developed insidiously during the last few months of 1934. It was first noted that he became more seclusive; this was followed by ideas of reference and persecution. He began to eat poorly and slept little. It was also noticed that he started to talk to himself at night.

Examination.—On admission, the physical findings were essentially normal. The urine showed nothing abnormal, and the serologic reactions of the blood were negative.

The mental picture was that of muteness; he sat or stood in one position for hours, showed negativism and seemed out of touch with the environment. He soon refused food entirely, and it was necessary to feed him by tube. He also presented incontinence of urine and feces.

Diagnosis.—The condition was diagnosed as dementia praecox of the catatonic type.

Course.—The subsequent course of the illness was characterized by a change of behavior resembling the hebephrenic more than the catatonic type of dementia praecox. After six months of muteness and negativism, the patient began to talk spontaneously, laughed in a silly manner, showed peculiar facial grimaces, answered questions in an incoherent and irrelevant manner, masturbated openly and smeared himself with food and feces.

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† Dr. Becker died May 4, 1939.

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Although aware that the prognosis in this case was probably poor, because of pressure on the part of the relatives we decided to treat him by means of metrazol shock. Careful physical examination revealed that his general condition was good.

On Nov. 23, 1937, 4 cc. of a 10 per cent solution of metrazol was given intravenously as the initial dose. Within fifteen seconds the patient had a typical clonic-tonic-clonic seizure, of about thirty seconds' duration. After the seizure the patient's respiration was irregular and somewhat labored. In a few minutes myoclonic movements were noticed on the left side of the face, followed by another spontaneous clonic-tonic-clonic convulsion. The respirations were noted to be even more disturbed, but the pulse remained full and regular. It was evident that considerable mucus was present in the throat; in addition, auscultation, though difficult, indicated signs of pulmonary edema. The twitchings of the left side of the face started again in a few minutes, and the jerkings continued to spread. Within ten minutes another generalized clonic-tonic-clonic seizure followed, which with little interruption developed into a state of continuous convulsions. By this time there was considerable respiratory embarrassment, and the pulse was rapid and feeble. Sodium amytal, 7½ grains (0.487 Gm.), was slowly injected intravenously, and all visible signs of muscular activity disappeared. The pulse improved immediately, but the pulmonary condition tended to persist, as was evidenced by the auscultatory signs: rapid and irregular respiration and cyanosis. A hypertonic solution of dextrose (20 cc. of a 50 per cent solution) given intravenously seemed to initiate rapid improvement. The patient slept about two hours, with no further untoward signs. On fully awakening he showed no residual symptoms and spontaneously assumed his previous habits.

Comment.—Careful search for the possible cause of this severe complication was immediately instituted. Physical and neurologic examinations were repeated, but no abnormal signs were elicited. The blood pressure was 128 systolic and 80 diastolic, and the pulse rate averaged about 75. The blood findings were: hemoglobin, 90 per cent; red cells, 5,000,000; white cells, 12,600; polymorphonuclear leukocytes, 57 per cent; lymphocytes, 40 per cent; mononuclears 1 per cent, and eosinophils, 2 per cent. The urine was entirely normal. Blood chemical studies showed: sugar, 90 mg.; nonprotein nitrogen, 27.7 mg.; urea, 12 mg.; creatinine, 1.1 mg.; uric acid, 2.8 mg.; cholesterol, 142.8 mg.; chlorides, 459.1 mg., and calcium, 9.9 mg. per hundred cubic centimeters. Stereoscopic roentgenograms of the skull were normal. Since there were no contraindications, a pneumoencephalogram was taken, but failed to reveal anything abnormal. The spinal fluid pressure was normal. Studies of the spinal fluid revealed negative Wassermann and Kahn reactions, a colloidal gold curve of 1100000000, a negative reaction to the Ross-Jones test, 57.1 mg. of sugar, 20.8 mg. of nonprotein nitrogen and 726 mg. of chlorides per hundred cubic centimeters.

A partial electroencephalographic study, which consisted of one sample taken from the right central region of the head, failed to show the abnormal rhythm which is described for grand mal or petit mal attacks. Intravenous injection of a subconvulsive dose of metrazol (1.5 cc.) did not materially change the wave potentials of the brain.[1]

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1. Hall, G. E.: Physiological Studies in Experimental Insulin and Metrazol Shock: Composite Preliminary Study by Members of the Department of Medical Research, Banting Institute, University of Toronto, Am. J. Psychiat. **95**:553 (Nov.) 1938.

In order to determine whether the smallest dose of metrazol required to provoke a seizure would also induce status epilepticus, the injections were resumed, starting with 1 cc. of the solution and advancing by increments of 0.5 cc. daily. At the initial injection of 1 cc. dilatation of the pupils and slight movements of the eyelids were the only recognizable physical signs. On the next day 1.5 cc. produced only the same signs. Three days later, 2 cc. caused marked dilatation of the pupils, blepharospasm and slight involuntary movements of the head and right leg. Two days later 2.5 cc. of metrazol gave rise to the following sequence: In about thirty seconds the right leg started to twitch; the head deviated to the left, and there followed immediately a clonic and then a prolonged tonic-clonic convulsion, which lasted about one and a half minutes. The patient suffered from respiratory embarrassment similar to that described for the original seizure. Ten minutes after the convulsion the patient was still in coma, with the eyes and head deviated to the left, the pulse strong but the respirations somewhat irregular. The deep reflexes were exaggerated bilaterally; the superficial reflexes were absent; there were a positive Babinski sign bilaterally and moderately coarse horizontal nystagmus. Ten minutes later the neurologic signs were about the same; however, the patient responded feebly to verbal and motor stimulation. There was still evidence of pulmonary embarrassment. In a few minutes he was observed manipulating his penis with his right hand. Shortly after, the patient's head suddenly deviated to the left, followed by continuous clonic jerks of the left arm, right leg and facial muscles. The attack was immediately interrupted by intravenous administration of sodium amytal (7.5 grains). Pulmonary embarrassment responded to 20 cc. of a 50 per cent solution of dextrose. The subsequent course was uneventful, and within two hours he was fully awake. Neurologic examination after the patient became conscious showed no abnormal features.

GENERAL DISCUSSION

Reports in the literature [2] suggest that patients with lesions of the central nervous system or with a known convulsive tendency react with smaller doses of metrazol than do others. It is our opinion that these causes for a lowered threshold to metrazol have been ruled out as far as is possible in this case. In spite of such careful study, the possibility of continuous convulsions occurring in the routine application of the drug in the treatment of the psychoses must be considered with other possible complications.

It should be emphasized that in this case the initial dose of a relatively small amount of the drug (4 cc. of a 10 per cent solution) brought about the state of continuous convulsions. This is significant, since most authorities [3] have agreed that from 3 to 5 cc., given intravenously, should be the usual initial dose.

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2. Langelüddeke, A.: Ueber die differentialdiagnostische Bedeutung der Cardiazolkrämpfe, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:203 (Sept.) 1936. Schönmehl, R.: Provokation von epileptischen Krampfanfällen, München. med. Wchnschr. **83**:721 (May 1) 1936.

3. von Meduna, L., and Friedman, E.: The Convulsive-Irritative Therapy of the Psychoses: Survey of More Than Three Thousand Cases, J. A. M. A. **112**: 501 (Feb. 11) 1939.

It is apparent that one should be prepared at all times to deal with this possible, though rare, complication. Excellent results were obtained with intravenous administration of sodium amytal [4] and hypertonic solution of dextrose.

CONCLUSIONS

1. Status epilepticus must be considered as a possible, though apparently rare, complication in the routine intravenous administration of metrazol.

2. The complication may occur at the initial administration of 3 or 4 cc. of the drug intravenously, as is recommended in the treatment for the psychoses.

3. Intravenous administration of sodium amytal and hypertonic solution of dextrose is found effective in controlling the status epilepticus.

4. Bryan, L. L.: Technique of the Insulin Shock and Metrazol Treatments, Psychiatric Quart. **13**:96 (Jan.) 1939. Beckenstein, N.: Results of Metrazol Therapy in Schizophrenia, ibid. **13**:106 (Jan.) 1939. von Meduna and Friedman.[3]

THE EXTERNAL GENICULATE BODIES

Degeneration Studies Following Occipital Lobectomy

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The presence of macula-sparing hemianopia after lesions of the occipital lobe is not an uncommon finding. Localized areas of softening in the anterior portion of the calcarine fissure without involvement of the optic radiation produce this type of defect in the visual field and may be readily explained by the absence of pathologic changes in the macular area at the posterior portion of the calcarine fissure and the occipital pole (Brouwer [1]). However, the appearance of macula-sparing hemianopia after destructive lesions of the occipital pole or subtotal occipital lobectomy requires some other interpretation. Two theories are available to explain the retention of macular vision in these cases: (1) a bilateral macular representation in the calcarine area and (2) an extensive macular representation not entirely confined to the occipital pole. The first theory was proposed by Lenz [2] and has some confirmation in the results of myelinogenic studies by Pfeifer.[3] Putnam [4] was unable to verify Pfeifer's description of a crossing tract in the splenium of the corpus callosum. Foerster's [5] report of a case in which macula-splitting hemianopia followed partial occipital lobectomy and section of the splenium of the corpus callosum added clinical evidence in favor of bilateral cortical representation of the macula. This theory was

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1. Brouwer, B.: Projection of the Retina on the Cortex in Man, A. Research Nerv. & Ment. Dis., Proc. **13**:529, 1932; Ueber die Projektion der Makula auf die Area striata des Menchen, J. f. Psychol. u. Neurol. **40**:147, 1930.

2. Lenz, G.: Zur Pathologie der zerebralen Sehbahn unter besonderer Berücksichtigung ihrer Ergebnisse für die Anatomie und Physiologie, Arch. f. Ophth. **72**: 1 and 197, 1909.

3. Pfeifer, R. A.: Myelogenetisch-anatomische Untersuchungen über den zentralen Abschnitt der Sehleitung, in Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie, Berlin, Julius Springer, 1925, no. 43.

4. Putnam, T. J.: Studies on the Central Visual System: II. A Comparative Study of the Form of the Geniculostriate Visual System of Mammals, Arch. Neurol. & Psychiat. **16**:285 (Sept.) 1926; III. The General Relationships Between the External Geniculate Body, Optic Radiation and Visual Cortex in Man, ibid. **16**: 566 (Nov.) 1926; IV. The Details of the Organization of the Geniculostriate System in Man, ibid. **16**:683 (Dec.) 1926.

5. Foerster, O.: Beiträge zur Pathophysiologie der Sehbahn und der Sehsphäre, J. f. Psychol. u. Neurol. **39**:463, 1929.

used by Penfield and Evans [6] and Penfield, Evans and MacMillan [7] to explain the retention of macular vision after subtotal occipital lobectomy. The theory of an extensive macular representation in the calcarine area was utilized by Fox and German [8] to explain similar macula-sparing hemianopias following partial occipital lobectomies. Brouwer's [9] experimental and clinical pathologic studies of the visual centers and pathways led him to the conclusion that the macular representation in the calcarine area must be extensive.

The representation of the retinal quadrants and the macula in the external geniculate body of man and apes has been well demonstrated by Rønne,[10] Brouwer and Zeeman,[11] LeGros Clark and Penman,[12] Brody [13] and Juba.[14] The macula is represented by a wedge-shaped intermediate segment extending from the caudal extremity of the external geniculate body almost to its anterior margin.

Studies of retrograde degeneration in the external geniculate bodies following pathologic or experimental lesions of the calcarine cortex or optic radiation by Brouwer,[1] Poljak and Hayashi,[15] Putnam,[4] Juba [16] and others have served to identify certain areas in the external geniculate bodies with discrete portions of the calcarine cortex or optic radiation. Lesions of the posterior portion of the calcarine cortex are followed

6. Penfield, W., and Evans, J.: Functional Defects Produced by Cerebral Lobectomies, A. Research Nerv. & Ment. Dis., Proc. **13**:352, 1932.

7. Penfield, W.; Evans, J. P., and MacMillan, J. A.: Visual Pathways in Man with Particular Reference to Macular Representation, Arch. Neurol. & Psychiat. **33**:816 (April) 1935.

8. German, W. J., and Fox, J. C.: Observations Following Unilateral Lobectomies, A. Research Nerv. & Ment. Dis., Proc. **13**:378, 1932. Fox, J. C., and German, W. J.: Macular Vision Following Cerebral Resection, Arch. Neurol. & Psychiat. **35**:808 (April) 1936.

9. Brouwer, B.: Anatomical, Phylogenetical and Clinical Studies on the Central Nervous System, in the Herter Lectures of the Johns Hopkins University, Baltimore, Williams & Wilkins Company, 1926, vol. 17, p. 1; footnote 1.

10. Rønne, H.: Die anatomische Projektion der Makula im Corpus geniculatum externum, Ztschr. f. d. ges. Neurol. u. Psychiat. **22**:469, 1914.

11. Brouwer, B., and Zeeman, W. P. C.: Experimental Anatomical Investigations Concerning the Projection of the Retina on the Primary Optic Centers in Apes, J. Neurol. & Psychopath. **6**:1, 1925.

12. LeGros Clark, W. E., and Penman, G. G.: The Projection of the Retina in the Lateral Geniculate Body, Proc. Roy. Soc., London, s.B **114**:291, 1934.

13. Brody, B. S.: Preliminary Investigation Concerning the Representation of the Fovea in the External Geniculate Body of the Monkey, K. Akad. v. Wetensch. te Amsterdam, Versl. **36**:1, 1934.

14. Juba, A.: Beiträge zur funktionellen Gliederung des Corpus geniculatum laterale des Menschen, Arch. f. Psychiat. **108**:85, 1938.

15. Poljak, S.: Projection of the Retina upon the Cerebral Cortex, Based upon Experiments with Monkeys, A. Research Nerv. & Ment. Dis., Proc. **13**:535, 1932. Poljak, S., and Hayashi, R.: The Cerebral Representation of the Retina in the Chimpanzee, Brain **59**:51, 1936.

16. Juba, A.: Die kortikale Doppelvertretung der Makula und die Projektion der Sehrinde auf den äusseren Kniehöcker des Menschen, Klin. Monatsbl. f. Augenh. **93**:595, 1934.

by degeneration of the cells occupying the macular representation in the external geniculate body. Therefore, if the macula is bilaterally represented in the calcarine cortex, unilateral excision or destruction of the cortical macular representation should result in bilateral secondary degenerative changes in the macular portion of the external geniculate body. There have been few reports on the condition of the contralateral external geniculate body following lesions of the calcarine area or optic radiation. Putnam [4] could find no evidence of degeneration in the contralateral geniculate body after an extensive occipital lesion that produced almost complete degeneration of the homolateral external geniculate body. Poljak [15] was likewise unable to demonstrate secondary degeneration in the contralateral geniculate body of monkeys after experimental lesions of the visual cortex. However, Juba [16] reported a case in which secondary degeneration was observed in the contralateral geniculate body and which was interpreted by him as evidence of bilateral cortical macular representation. Unfortunately, this patient had bilateral cataract, preventing adequate examination of the fundi and visual fields, and the pathologic description failed to eliminate completely the possibility of a primary macular lesion in the retina. Further evidence on this question has recently been contributed by the experimental studies of Maison, Settlage and Grether.[17] These workers found complete cortical blindness in monkeys after unilateral occipital lobectomy and section of the contralateral optic tract. They concluded that crossing of macular fibers or their collateral branches through the splenium of the corpus callosum to the contralateral occipital cortex does not occur in the monkey.

The present report is based on the study of serial sections of the contralateral external geniculate body after right occipital lobectomy for localized metastasis of a sarcoma in the posterior portion of the occipital lobe. The pathologic material was obtained by postmortem examination ten weeks after the operation, and the patient was known to have had left homonymous macula-sparing hemianopia at least five weeks before operation. The minimal total duration of the combined surgical and pathologic lesion was therefore fifteen weeks.

REPORT OF A CASE

History.—M. B., a woman aged 41, entered the hospital on Sept. 17, 1936, because of headache and visual disturbances of three weeks' duration. She had lost 25 pounds (11.3 Kg.) in weight during the preceding nine months and had noted weakness for three months. Severe right frontal pain began three weeks before admission and was associated with nausea and vomiting. A defect in the left visual field was noted by the patient at the same time. During the three weeks prior to admission to the hospital she observed slight red discoloration in two specimens of urine.

Examination.—Physical examination revealed a large, nontender mass in the left upper quadrant of the abdomen, which moved freely on respiration and was palpable as far posteriorly as the left costovertebral angle. Tangent screen perimetry

17. Maison, G. L.; Settlage, P., and Grether, W. F.: Experimental Study of Macular Representation in the Monkey, Arch. Neurol. & Psychiat. **40**:981 (Nov.) 1938.

demonstrated left homonymous hemianopia with sparing of the macula. Visual acuity was normal, and there were no signs of increased intracranial pressure. Neurologic examination otherwise gave normal results. Roentgenograms of the skull demonstrated a slight increase in the convolutional markings. Roentgenograms of the chest showed several areas of increased density which were interpreted as metastatic tumor nodules in the lungs. Roentgenograms of the abdomen revealed a large soft tissue shadow in the region of the left kidney. Intravenous pyelograms showed obliteration of the upper portion of the pelvis of the left kidney. A cystoscopic specimen of urine from the left ureter contained blood. The clinical diagnosis was malignant tumor involving the left kidney, probably a hypernephroma, with metastases to the lungs and to the right occipital lobe.

Treatment and Operation.—The patient was given roentgen therapy to the abdominal tumor, receiving a total of 3,250 roentgens through three fields. Because of intractable headache, a direct surgical attack on the metastatic lesion in the right occipital lobe was undertaken on October 22. The right occipital lobe was exposed through an osteoplastic bone flap in the right occipitoparietal region, and two large areas of discoloration were identified on the lateral surface of the occipital lobe. One was well posterior, in about the location of area 18 of Brodmann, and was yellow brown. The other was somewhat more anterior, in the approximate location of area 19, possibly extending into area 39, and was of the same color. They obviously represented bleeding into the cortical tissue. The pia-arachnoid and the dura were likewise stained yellow in this region. The cortex was transected over the anterior discolored area, and a large quantity of blood clot was evacuated. The occipital lobe was resected at a point just posterior to the junction of the calcarine and the occipitoparietal fissure. The surgical specimen weighed 92 Gm. and measured 7 by 7 by 4 cm. It contained a large hemorrhagic cavity and a firm granular tumor, the latter measuring 2.5 cm. in diameter. The tumor was a metastatic neurocytoma.

Postoperative Course.—Postoperative roentgen therapy was given to a subcutaneous tumor nodule in the left occipital region, a total of 2,250 roentgens being delivered over a period of eighteen days. The immediate postoperative course was satisfactory, but early in November headaches recurred and were soom accompanied by vomiting and the appearance of signs of cerebellar involvement. Intermittent hematuria was noted during the remainder of the patient's stay in the hospital, but the headaches and cerebellar signs subsided to a considerable degree. Repeated roentgenograms of the chest revealed an increase in the size of the metastatic tumor nodules in the lungs. Death occurred on December 27, approximately fifteen weeks after admission to the hospital and ten weeks after operation.

Autopsy.—Postmortem examination revealed marked emaciation. A large, firm tumor was located in the left perirenal region and involved the major portion of the left kidney. Tumor metastases were observed in the scalp, lungs, pancreas, right kidney and superior mediastinal lymph nodes. Tumor invasion was demonstrated in the left renal veins and renal pelvis. A metastatic tumor nodule, 2 cm. in diameter, was seen in the left cerebellar hemisphere. No other metastases were identified in the brain. The site of the occipital lobectomy was verified (fig. 1 *A*); it was found to be just posterior to the junction of the occipitoparietal and the calcarine fissure. A distance of 2.2 cm. separated the level of transection from the splenium of the corpus callosum. The stria of Gennari was identified grossly and microscopically at the anterior extremity of the stem of the calcarine fissure, at about the level of the splenium of the corpus callosum. Serial sections of the left

external geniculate body and of the superior colliculi were stained by the Nissl method. Serial sections of the right (homolateral) external geniculate body were stained by the Nissl method and with hematoxylin and eosin.

The right (homolateral) external geniculate body was the seat of extensive secondary degeneration of ganglion cells (fig. 1*B*). The normal laminated

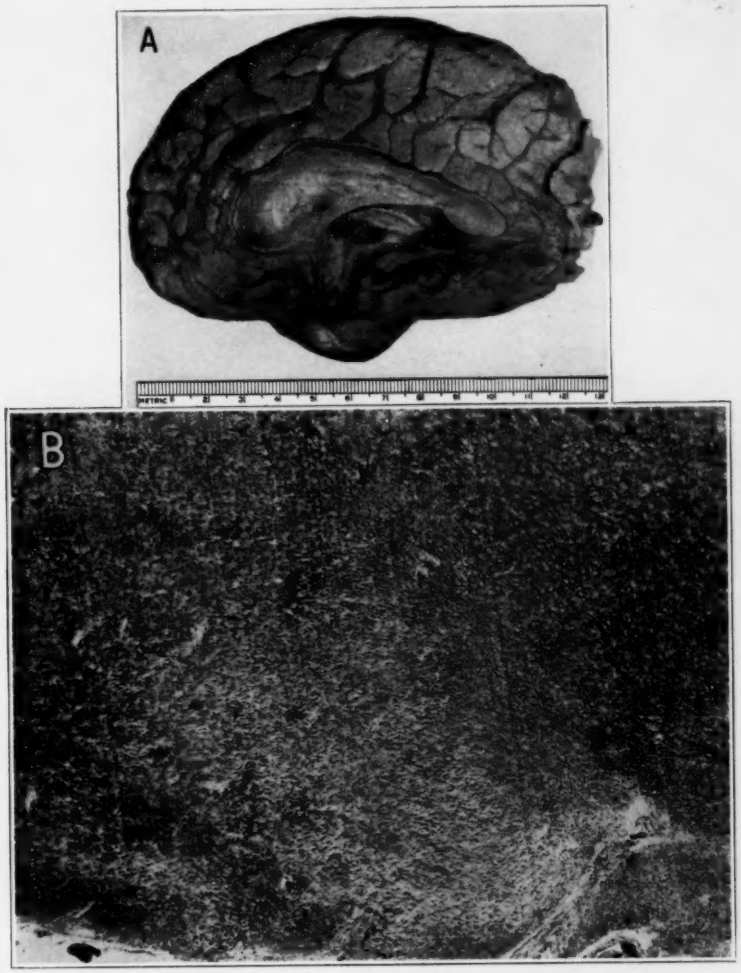

Fig. 1.—*A*, medial aspect of the right cerebral hemisphere, showing level of occipital lobectomy. The occipitoparietal sulcus has been spread to facilitate its identification. *B*, section through the right (homolateral) external geniculate body. Hematoxylin and eosin stain; × 22.

architecture was partially obliterated by gliosis, and only occasional ganglion cells with a semblance of normal appearance could be found.

The left (contralateral) external geniculate body showed no demonstrable evidence of secondary degenerative changes in the ganglion cells (fig. 2). The

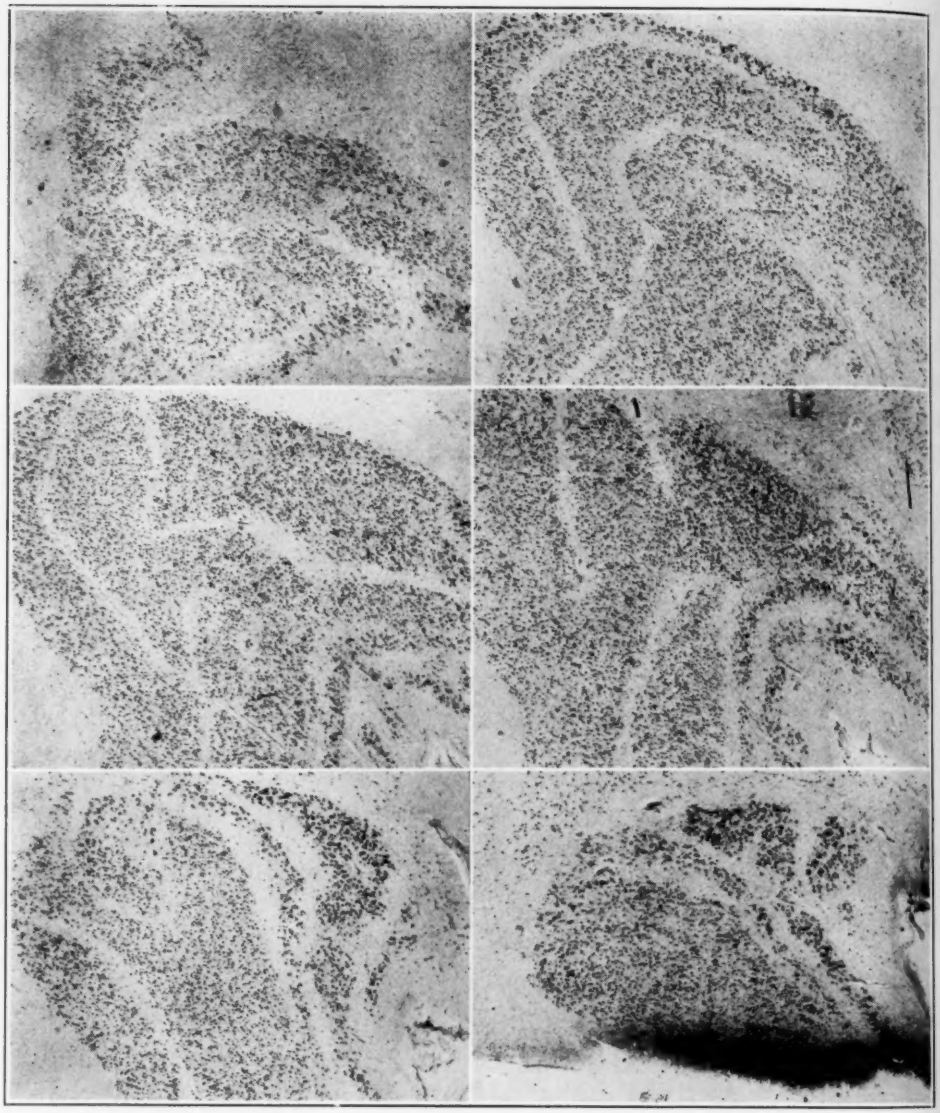

Fig. 2.—Representative sections through the left (contralateral) external geniculate body. Sections were cut 5 microns in thickness; every fifth section was mounted. Sections were numbered from rostral to caudal. Upper row: left, no. 10; right, no. 60. Middle row: left, no. 105; right, no. 130. Lower row: left, no. 170; right, no. 190. Nissl stain; × 22.

architecture was normal, with the usual laminated appearance, and no areas of cellular depopulation, shrinkage or abnormality of staining characteristics could be identified.

Study of serial sections of the superior colliculi failed to reveal any abnormalities within these structures.

The primary tumor and its metastatic nodules were composed of a dense fibrillary stroma of connective tissue containing spindle-shaped cells, many of which exhibited polar processes which contributed to the formation of the stroma. A few of the cells were in mitotic division, and many were pyramidal, while others were round and resembled lymphocytes. Acinar formation was absent, and there was no evidence of vacuolated cytoplasm. Axis-cylinders were identified in the tumor, but myelin sheaths were absent.

The pathologic diagnosis was neurocytoma.

COMMENT

In spite of the presence of extensive degenerative changes in the cells of the homolateral external geniculate body, no evidence of secondary degeneration was observed in the contralateral geniculate body. These results are in accord with the observations of Putnam [4] in man and of Poljak [15] in monkeys. They are at variance with the findings of Juba,[16] who suggested that Putnam [4] and Poljak [15] probably failed to find contralateral secondary degeneration because sufficient time had not elapsed for contralateral degenerative changes to occur and because these contralateral degenerative changes are less striking than those observed on the homolateral side. No doubt the same objection could be offered to the results of the present study. However, it is difficult to understand why contralateral degeneration should be completely absent while homolateral changes are extremely marked unless bilateral cortical macular representation occurs by collateral branching of the neurons composing the macular portion of the optic radiation. The argument against bilateral cortical macular representation in the monkey appears rather well established by the failure of Poljak [15] to find any evidence of collateral branching of the fibers of the optic radiation and by the work of Maison, Settlage and Grether,[17] who showed that if such a hypothetical tract exists it must leave the optic radiation posterior to the level of their occipital resections. The present study suggests that bilateral cortical macular representation in man is improbable unless the presence of collateral branching of the macular fibers is assumed.

SUMMARY AND CONCLUSION

1. No evidence of secondary degenerative changes could be found in the contralateral geniculate body ten weeks after subtotal occipital lobectomy, and fifteen weeks after perimetric demonstration of macula-sparing hemianopia. Extensive secondary degenerative changes were identified in the homolateral external geniculate body.

2. The absence of secondary degenerative changes in the contralateral external geniculate body suggests that bilateral cortical macular representation does not occur in man unless collateral branching is present in the macular fibers of the optic radiation.

DISCUSSION

DR. WILLIAM J. GERMAN, New Haven, Conn.: We have been pursuing the elusive problem of bilateral macular representation in the calcarine area for several years and thought that perhaps we had it cornered at this point. However, there still seems to be an "if" in the question; that is, as Dr. Brody concluded, it seems unlikely that bilateral macular representation exists in the calcarine area unless collateral branching occurs.

The recent experimental work of Maison, Settlage and Grether, I think, is particularly pertinent. Their work, as Dr. Brody mentioned, consisted of occipital lobectomy on one side and section of the optic tract on the other. It seemed logical that if bilateral macular representation occurred in the experimental animal which was used—the Macacus rhesus monkey—there should be some cortical vision remaining. They concluded that bilateral macular representation in the rhesus monkey could be ruled out by their experiments, unless this hypothetic crossing tract took a far backward turn. It would seem that the degeneration studies which have just been reported would rather exclude the likelihood of a fair backward turn of the hypothetic crossing tract.

DR. TRACY J. PUTNAM, New York: The subject of the alleged bilateral representation of the macula has been a hardy perennial at neurologic meetings, but I believe the matter is now on the verge of being settled, thanks to this excellent presentation and to two other communications which are pending.

At the risk of being repetitious, I should like to emphasize once more that the conception of the bilateral representation of the entire macula is a purely clinical one. No one who has thoroughly studied anatomic, pathologic or experimental material has championed it. Not only Dr. German's case but also the carefully studied and well adapted cases of Meyer, Brouwer and others and those that I reconstructed in Professor Brouwer's laboratory are definitely opposed to the conception.

An anatomist, Pfeifer, and a pathologist, Juba, have been cited as favoring the theory. Pfeifer in his most recent publication averred that he had never stated that there was a crossed macular bundle but that he had stated that if such a bundle existed it was displayed in the brain of the infant whose case he was reporting. When I reconstructed the tract in a similar brain, prepared by Professor Brouwer, and did not find a callosal bundle, Pfeifer's criticism was that I had not followed the fibers he had indicated under a high power lens. However, I did follow the fibers in each section of a complete series with great care, and they ended in the striate cortex.

Juba's case is also cited as evidence of bilateral representation. It was that of a patient with a large area of softening in the left occipital lobe. Serial sections of this lobe showed miliary softening also. There was atrophy in both corpora geniculata, severe in the left and mild in the right. But the right occipital lobe was apparently not even sectioned. Obviously, there was presumably miliary softening in it also.

The clinical evidence has been wholly unsatisfactory. In regard to the famous case reported by Foerster, in which the splenium was cut and complete left hemianopia ensued, the fact is often overlooked that the right occipital lobe was retracted to expose the quadrigeminal bodies. Vigorous retraction must therefore have been applied at the anterior extremity of the calcarine fissure. As a result, 5 cm. of the occipital lobe had to be resected. Small wonder that its function was impaired. Moreover, the patient was irrational at the time the fields were taken.

More significant, it seems to me, than this highly doubtful case, is one which Dr. Hyndman has recently observed. A patient had partial hemianopia from a tumor. In the course of the operation the splenium had to be divided; after operation an undoubted remnant of vision was demonstrated in the blind field. I am careful to say a "remnant of vision," because in none of the cases reported has the retained central vision actually corresponded to the size of the fovea. It has varied in size from 1 to 20 degrees.

The literature on this subject is being reviewed by Dr. Liebman, and much of it is an amazing tangle of misconception.

One point is clear from the recent work of Dr. German and others which was still obscure at the time I reconstructed Professor Brouwer's cases fifteen years ago, and that is the forward extent of the fibers subserving central vision. They are evidently not confined to the occipital pole, though doubtless they are most numerous there, but must lie in the depths of the calcarine fissure well up to its anterior extremity.

Dr. James C. Fox Jr., New Haven, Conn.: This contribution constitutes another bit of negative evidence about the question of bilateral representation of central vision. It is my belief that practically all the clinical facts obtained by perimetry in known lesions of the occipital lobe of various types, including the lobectomies, can be explained by diffuse representation of the macula. However, with respect to this particular work it seems that three questions might be asked. One has already been raised by the authors: If collateral neurons are present on the homolateral side, would not retrograde degeneration take place in the contralateral geniculate body? There is also the question of adequate time between the lobectomy and the pathologic examination. In experimental studies of animals retrograde degeneration takes from five to six months at least. I believe that Brouwer advocated this interval in studying retrograde degeneration in the cells of the ventrolatreal nucleus of the thalamus following cortical lesions. The authors have pointed out that the extensive degeneration on the homolateral side is significant, because one would also expect some degeneration on the contralateral side. However, there is also the tumor, which has been present for at least fifteen weeks and probably considerably longer. The degeneration found may have been entirely due to the destruction of the calcarine cortex by this lesion rather than a result of the lobectomy.

The third point that might be raised is the possibility that crossing fibers may terminate in the anterior portion of the striate cortex, in front of the level of the transection in this instance. The studies of von Economo have shown that the striate area extends much farther forward than is usually represented in diagrams of this region, in fact to a frontal plane falling at the level of the splenium. It is of course possible that if there are crossing fibers they might have terminated solely in this region and escaped injury.

Dr. Putnam discussed this problem so thoroughly that there is little to be added. However, there is one type of field defect which has never been explained by any theory of macular representation, namely the sector scotoma including the fixation point, which may occur with partial lesions of the calcarine cortex. It is interesting that such field defects usually occur after trauma, and all are of course familiar with the studies made by Holmes at the time of the Great War on gunshot injuries of the occipital lobe. It is also interesting that Dr. Cushing, in his paper on the visual field defects associated with lesions of the temporal lobe delivered before this association in 1921, reported several cases of quadrantic scotomas including the fixation point. Those also occurred in association with trauma and not with neoplasm, in which the field defects were always more rounded. One must admit that the

problem of central vision has not yet been solved, nor does any one theory of macular representation explain all the facts.

Dr. Olan R. Hyndman, Iowa City, Iowa: The patient to whom Dr. Putnam made reference was a man of middle age who presented evidence of a tumor of the third ventricle on ventriculographic examination. In spite of the increased intracranial tension and papilledema, the patient presented full visual fields, visual acuity of 6/6 in one eye and 6/9 in the other. An occipital flap was turned down with the intention of approaching the tumor through the corpus callosum, but at the first operation the brain was so tense that I felt it would be wiser to resect the right occipital lobe as a preliminary stage. The occipital lobe was resected through a plane just about tangent to the posterior tip of the splenium. The patient recovered from this operation, and his visual fields then presented a left homonymous hemianopia with sparing of central vision. About one week later, under local anesthesia, the brain was reexplored, and the corpus callosum was sectioned 2¼ inches (5.7 cm.) from the posterior tip of the splenium. Biopsy showed that the tumor was a gliomatous tumor, and nothing further was done. The patient recovered so quickly from this procedure that on the third day more visual fields were taken, with particular reference to central vision; and it was rather striking that not only did he present split central vision but there seemed to be complete central scotoma. The test was repeated several times at intervals of a few minutes to allow him to rest, and the same field was obtained each time. Nine days later another visual field was taken, showing complete recovery of central vision, and one month later another field showed the same condition. Visual acuity returned to 6/6 in one eye and 6/9 in the other.

It is interesting to speculate why on the third day this man presented almost complete scotoma for central vision. It was necessary to retract with a spatula the mesial cortex anterior to the calcarine fissure, not only on the right side but also on the left side, in order to section the splenium. This retraction might have been responsible for a temporary loss of function, and the result might indicate that macular vision or central vision has some representation in the mesial cortex anterior to the calcarine area. In recalling Foerster's case, it might perhaps explain why he too found split macular vision.

Dr. William J. German, New Haven, Conn.: Concerning Dr. Putnam's remark about terminology, I think it is conceded that we are measuring not macular vision but central vision. I think that the correction is a valuable one. With the other points made by Dr. Putnam we are completely in accord.

Concerning Dr. Fox's point on collateral branching of the macular fibers running to the striate cortex, we cannot rule out that possibility, as I mentioned previously. As to the factor of time interval, I can say only that since this was not an experimental setup we could not select our time interval. However, the homolateral external geniculate body was completely degenerated, and we could find no changes in the contralateral body; we believed that was significant.

As for the question of fibers crossing from the anterior end of the striate cortex: that is, of course, possible, but it seems that the necessity for assuming a contralateral representation no longer exists if one wishes to locate these crossing fibers in the anterior end of the striate cortex.

I am particularly interested in Dr. Hyndman's contribution. We had hoped to carry out a similar clinical experiment ourselves. However, our retraction on the stem of the calcarine fissure apparently was a little more severe than Dr. Hyndman's, since the hemianopia remained macular splitting after the first stage; so we were unable to carry on any further observations after section of the splenium. I think his clinical experiment perhaps will give the final answer which we have been seeking.

CESSATION OF EPILEPTIC SEIZURES AND THE ELECTROENCEPHALOGRAM

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The present communication is concerned with an analysis of the electroencephalographic tracings of a group of 38 institutionalized epileptic patients who had been observed daily for ten or more years and who had not had a seizure for the past five to thirty years. Selected from 1,500 epileptic patients, these 38 persons were the only ones who had been totally free from seizures for five or more years.

Only 1 of the patients had been receiving phenobarbital, 1½ grains (0.0975 Gm.) daily. None of the remaining patients had received anticonvulsant therapy for the past five or more years.

The ages of the patients ranged from 17 to 74 years. In the second decade there were 5 patients; in the third, 10 patients; in the fourth, 7 patients; in the fifth, 3 patients; in the sixth, 6 patients; in the seventh, 5 patients, and in the eighth, 2 patients.

The intelligence quotient varied from 10 to 76, only 1 patient having a rating above 60.

Seven patients had an intelligence quotient under 30; 6 had a rating of 30 to 40; 7, a rating of 40 to 50, and 8, a rating of 50 to 60. It was not possible to determine the intelligence quotient in 9 cases.

On the basis of diagnosis, the patients fell into the following groups: idiopathic epilepsy, 22; symptomatic epilepsy, 13 (epilepsy as the result of trauma to the head, 3), and epilepsy of unknown origin, 3. A hereditary background of migraine or epilepsy was present in 10 cases.

The duration of the disease preceding the last seizure varied from two to forty-eight years.

There was no known factor to which cessation of seizures could be attributed.

Electroencephalographic records of each person were obtained while the patient rested quietly and then again while he hyperventilated for at least three minutes. Some of the patients could not be induced to hyperventilate, or did so in so superficial a manner that the record was considered as a resting one.

Records were classified as abnormal provided there was present one or more of the following formations: fast activity consistent with grand mal, wave and spike, waves with a frequency of less than 6 per second and numerous 6 per second waves. Only 3 patients showed wave and spike formations, and this only on hyperventilation. In addition to the wave and spike pattern, these records showed slow activity. The slow activity (waves of 5 or less per second) was the predominant abnormality in all the aberrant records.

Of the total of 38 epileptic patients who had not had seizures for five or more years, the electroencephalographic records of 25, that is, of 65 per cent of the group, were abnormal. The patient receiving anticonvulsant therapy also had an aberrant record.

From the Monson State Hospital, Palmer, Mass., and the Department of Neuropathology, Harvard Medical School, Boston.

There was no correlation between the incidence of abnormal electroencephalographic records and the type of epilepsy, the intelligence quotient or the age. It was also surprising to find that there was no significant difference in the incidence of abnormal records among patients who have not had seizures for five years and those without seizures for a longer period.

The importance of hyperventilation in establishing the abnormality of an electroencephalographic record is demonstrated by the fact that 10 patients had normal records until they overbreathed.

Eleven patients were unable to hyperventilate at all, or did so inadequately (i. e., only two or three deep respirations). Nevertheless, 7 of them had an abnormal resting record. The 4 who did not hyperventilate and whose resting record was normal might conceivably have shown significant changes on hyperventilation. But even with this group rated as normal electroencephalographically, there is a large percentage (65) of abnormal records in the entire series. Analysis of the records of the 27 patients without seizures who did hyperventilate revealed that 18 had abnormal electroencephalograms, an incidence of 66 per cent, which is a close check. None of the patients who hyperventilated had seizures. Thus, it is evident that an electroencephalogram may be helpful in the diagnosis of epilepsy in persons who several years before have had a poorly defined "spell," the nature of which is obscure.

SUMMARY

An analysis is presented of the electroencephalographic records of 38 institutionalized epileptic patients who had not had seizures for from five to thirty years.

All but 1 of the patients had been without medication during this time. The one who had received anticonvulsant therapy (phenobarbital, 1½ grains daily) also had an abnormal electroencephalographic tracing.

The ages ranged from 17 to 74 years.

The intelligence quotient ranged from 10 to 76.

The electroencephalographic record was abnormal in 25 patients, or 65 per cent of the group.

There was no correlation between the incidence of abnormal electroencephalograms and the type of epilepsy, the intelligence quotient, the age or the length of time during which patients had been free from seizures.

Abstracts from Current Literature

Physiology and Biochemistry

A Law of Denervation. Walter B. Cannon, Am. J. M. Sc. **198**:737 (Dec.) 1939.

Cannon propounds a law of denervation to the effect that when in a series of efferent neurons a unit is destroyed, increased irritability to chemical agents develops in the isolated structure or structures, the effect being maximal in the part directly denervated. An illustration of this law is that after unilateral paralysis of the dilator muscle of the iris following section and degeneration of its stimulating fibers, the pupil in certain conditions is more widely dilated on the paralyzed than on the normal side—so-called paradoxic pupillary dilation. By sensitization is meant that the dose of the substance required to yield a certain submaximal response after the operation is smaller than before. An effect quite as remarkable as sensitization by cutting the ultimate adrenergic fibers is moderate sensitization by cutting preganglionic fibers. Severance of either stimulatory or inhibitory adrenergic fibers is followed by sensitization of the denervated smooth muscle to natural chemical agents. Shen and Cannon showed that smooth muscle was sensitized to pilocarpine and acetylcholine by destruction of its cholinergic fibers. Past evidence is presented to show that structures such as the lacrimal and submaxillary glands and smooth muscle become more readily responsive to chemical agents when deprived of their nerve connections. Denervated structures become more responsive not only to the agents which are their natural stimulants, e. g., epinephrine and acetylcholine, but to other agents. Haimovici and Cannon demonstrated that, just as neurons of the superior cervical ganglion are sensitized by severance and degeneration of nerve fibers which routinely deliver impulses to them, neurons of the spinal cord are sensitized by partial exclusion of their normal nerve connections. Cannon raises the question whether it is not possible that tumors and such lesions of the motor area of the cortex as are associated with the name of Hughlings Jackson may induce instability of the neighboring cortical cells by destroying their connections with other cortical cells.

Michaels, Boston.

Cortical Spread of Epileptic Discharge and the Conditioning Effect of Habitual Seizures. Wilder Penfield and Edwin Boldrey, Am. J. Psychiat. **96**:255, 1939.

Penfield and Boldrey studied cortical stimulation in 165 cases in which craniotomy was performed and in most of which the diagnosis was focal epilepsy. They report 9 cases to illustrate atypical responses to stimulation of the cortex of epileptic patients. These atypical responses included displacement of aura by facilitation, sensory activation, distant sensory responses, isolated activation and epileptic spread. The points at which responses were obtained in these 9 cases were studied in correlation with the initial phase of the patient's seizures, and it was found that localization of the points of stimulation corresponded closely with the localization of simple representation. This was studied for induced seizures beginning with movement and sensation of the upper extremities, movements of the mouth and throat and vocalization.

Penfield and Boldrey state that the point of origin of induced seizures beginning with motor or sensory manifestations is in or near the corresponding motor or sensory zone. Distant responses are produced by lowering of the threshold for areas of the rolandic cortex, together with that of connecting links to this area.

Activation was evidenced by the eliciting of great responses from the rolandic cortex and from otherwise silent areas. The correlation between activation and conditioning is pointed out. The refractory state was found to be associated with postconvulsive paralysis or was quite independent of the paralysis. Distant responses were found in some cases to apply exclusively to the initial phenomenon, and in others not to be associated with the epileptic march. These distant responses were frequently associated with refractory states elsewhere. Distant responses of auras frequently were elicited from the area of the lesion, although on occasion no intervening responses could be demonstrated. The authors found that, except for refractory periods, the areas of cortex habitually subjected to seizure discharge have a lowered threshold. The occurrence of a seizure as a result of electrical stimulation depends on the strength of stimulation and on its duration. Penfield and Boldrey state that the seizure discharge begins in each case at a point in the brain adjacent to the electrode, and probably adjacent to an epileptogenic lesion, and that the spread of a seizure is from any particular point toward the rolandic fissure, this line of conduction being established by a conditioning process, which is reenforced by each succeeding epileptic discharge.

FORSTER, Boston.

PHYSIOLOGICAL STUDIES IN INSULIN TREATMENT OF ACUTE SCHIZOPHRENIA (CHOLINE ESTERASE). L. O. RANDALL and E. M. JELLINEK, Endocrinology **25**:279 (Aug.) 1939.

The choline esterase activity of the blood serum of 22 patients with acute schizophrenia was determined by the gasometric method of Ammon twice in the two weeks preceding and twice in the two weeks following treatment with insulin. The authors do not state the degree of shock or the number of comas induced during the insulin treatment. The choline esterase level of the patients was initially somewhat lower than that of the normal control subjects. By statistical test, however, this difference was not significant. After insulin treatment the choline esterase level increased significantly, irrespective of whether the patients recovered or not. In the "recovered" patients the intraindividual variation was greatly lessened after treatment, the function becoming stabilized, while in the patients who did not recover the intraindividual variation was significantly increased; i. e., the function became highly unstable. In both types of patients the increased choline esterase level tended to decrease toward the initial level in the second week following medication.

PALMER, Philadelphia.

PHYSIOLOGICAL STUDIES IN INSULIN TREATMENT OF ACUTE SCHIZOPHRENIA (THE BLOOD MINERALS). J. M. LOONEY, E. M. JELLINEK and C. G. DYER, Endocrinology **25**:282 (Aug.) 1939.

The potassium, calcium and phosphorus contents of the blood were determined for 22 schizophrenic patients four times in the two weeks preceding and four times in the two weeks following treatment with insulin. The authors do not give the duration of the insulin therapy or state the number and depth of comas induced during the period of treatment. The potassium and calcium contents showed no changes after medication. The mean level of the inorganic phosphorus of the blood was initially higher in the patients than in normal controls. The phosphorus level of the 10 patients who recovered dropped significantly to normal after treatment with insulin. The patients who did not recover, however, showed an insignificant decrease only. Thus it would appear that the elevation of the phosphorus level of the blood in acute schizophrenia is an important feature, and that its normalization by insulin is probably a significant element in the mechanism of remission. The decrease of inorganic phosphorus in the case of the "recovered" patients may be due to its better utilization in the formation of phosphorylated compounds.

PALMER, Philadelphia.

RADIOACTIVE PHOSPHORUS AS AN INDICATOR OF PHOSPHOLIPID METABOLISM. B. A. FRIES, G. W. CHANGUS and I. L. CHAIKOFF, J. Biol. Chem. **132**:23, 1940.

The deposition of labeled phosphatide at intervals of twenty-four and forty-eight hours after administration of radioactive phosphorus was employed to compare the phosphatide activities, or turnover, of the forebrain, cerebellum, medulla and spinal cord in the rat. The highest phosphatide activity is present on the day of birth in all parts of the central nervous system. From birth until the time the rat attains a weight of 50 Gm. a precipitous decline in phosphatide activity occurs in the entire central nervous system. So striking is this loss that by the time the rat reaches a weight of 50 Gm. the spinal cord retains only 5 per cent of the activity present in the newborn rat. An abrupt change in phosphatide activity occurs in the central nervous system of the rat between the times it reaches the weight of 30 and that of 50 Gm. As growth proceeds beyond 50 Gm. phosphatide activity decreases throughout the central nervous system, but at a much slower rate than was observed between birth and the time the rat reaches a weight of 50 Gm. The spinal cord in the 200 Gm. rat possesses an activity 20 per cent of that present in the 50 Gm. rat, whereas in the 300 Gm. rat the cord retains 15 per cent of the activity found in the 50 Gm. animal. The forebrain, cerebellum and medulla also lose activity as the weight of the animal increases from 50 to 300 Gm., but the rate of decline in activity is less than that which occurs in the cord. Phosphatide activity is not uniform throughout the central nervous system. It is highest in the spinal cord from birth to the time the rat reaches a weight of 50 Gm. After this the relative activities of forebrain, cerebellum and medulla rise steadily, and by the time a weight of 200 or 300 Gm. is attained they are as great in these divisions as in the cord, or even greater.

PAGE, Indianapolis.

STUDIES IN THE PHYSIOLOGY OF THE EMBRYONIC NERVOUS SYSTEM: I. EFFECT OF CURARE ON MOTOR ACTIVITY OF THE CHICK EMBRYO. ZING YANG KUO, J. Exper. Zoöl. **82**:371 (Dec.) 1939.

Curare dissolved in Locke's solution was injected into the amniotic cavity of 3 to 12 day chick embryos in order to determine the effect of the drug on spontaneous cardiac, amniotic and somatic movements and on movements elicited by electrical stimulation. All spontaneous somatic movements were abolished by sufficient doses, but there was no effect on the heart beat and the contraction of the amnion. At any given age the order of dissolution of movements of different parts of the body followed the order of prominence and activeness of the parts in movement at that age. In the 3 day embryo, curare tended to prevent the appearance of the first somatic movements. Every type of normal spontaneous movement could be elicited by electrical stimulation in the untreated embryo. Curarization prevented this. It is concluded that the spontaneous somatic movements and those elicitable by electrical stimulation in the chick embryo are neurogenic.

WYMAN, Boston.

THE LIGHT RESPONSE OF THE MARINE TUBIFICIA WORM, CLITELLIO ARENARIUS (O. F. MÜLLER). DWIGHT ELMER MINNICH, J. Exper. Zoöl. **82**:397 (Dec.) 1939.

Clitellio arenarius is a small worm living gregariously in the sand under stones between the tide levels, and is abundant on the shores of Mount Desert Island, Maine. Individual worms respond to a sufficient increase of illumination with coiling of the posterior two thirds of the body. Continued illumination causes no further coiling, but gradual extension instead. There is no response to a decrease in intensity of illumination. The evidence indicates that the photo-

receptors involved are somewhat diffuse in their distribution over the body. Prolonged exposure to intense illumination is injurious or fatal to Clitellio; hence, the response is protective. The reaction time to sudden illumination varies, up to a certain limit, directly as the logarithm of the intensity of the light. The sensory process consists of a short period of sensitization which requires light and a long latent period which does not require light. The reaction to increase of illumination varies in magnitude with the intensity of stimulation, thus indicating that numerous receptors are involved. The latent period is markedly affected by temperature. The course of dark adaptation in Clitellio is described by the equation of a bimolecular chemical reaction, and the temperature coefficient is that of an ordinary chemical reaction; hence, dark adaptation must be controlled by a chemical process.

WYMAN, Boston.

EXPERIMENTAL OBSERVATIONS ON HEADACHE. G. W. PICKERING, Brit. M. J. **1**:907 (May 6) 1939.

Pickering discovered that histamine produces severe headache when injected intravenously. This occurs even when the blood supply to the scalp is arrested by an Esmarch bandage, suggesting that the headache arises from the meninges and not from the scalp. A further confirmation is the fact that shaking the head makes the pain worse. Further, the pain seems to arise from structures supplied by the fifth nerve, since headache produced by histamine is confined to the normally innervated side in a patient with unilateral section of the trigeminal nerve. Pickering's second premise is that histamine probably acts on the intracranial blood vessels, since histamine affects chiefly smooth muscle. About fifteen seconds after an injection of histamine there are flushing of the face, a fall in arterial pressure and a rise in cerebrospinal fluid pressure, due to cerebral vasodilatation. The headache begins later, at about the first minute. It is maximal at about the second minute and disappears at about the eighth minute. This relation between the vascular events and the headaches is not fortuitous, for if histamine is infused intravenously for several minutes at a constant rate the headache is delayed until a minute or two after the infusion is discontinued. This suggests that something occurs during the stage of intense vasodilatation which prevents the appearance of headache. This is confirmed by the fact that a second injection of histamine given during a headache will abolish the headache until the vasodilating effect of the second injection has worn off. This effect of a second injection is due to vasodilatation, because the same transitory relief is achieved by another substance having similar dilatory properties, namely, amyl nitrite.

In the light of these and other experiments, the course of events following injection of histamine seems to be: The first stage is one in which dilatation of the small vessels predominates and in which the intracranial arteries, though probably relaxed, are prevented from dilating by the fall of arterial pressure inside and by the rise of intracranial pressure outside. During the second stage the arterial and intracranial pressures return to normal and dilatation of all small vessels subsides; coincidentally, the larger intracranial arteries, the walls of which are still relaxed, expand; it is this expansion which seems to give rise to headache. Finally, relaxation of the intracranial arteries passes off and headache subsides.

With this preamble, Pickering considers several clinical varieties of headache. It is suggested that the headache following removal of spinal fluid by lumbar puncture is the result of expansion of intracranial arteries due to the fall in pressure outside these vessels or to stretching the dural venous sinuses by a hyperemic and displaced brain. It is also suggested that the headache commonly observed in cases of acute infection may be due to stretching of the sensitive structures around the intracranial arteries, presumably arising from relaxation of these vessels.

ECHOLS, New Orleans.

OBSERVATIONS ON THE EFFECTS OF TRIGEMINAL DENERVATION. G. F. ROWBOTHAM, Brain **62**:364, 1939.

In a group of 50 patients operated on for trigeminal neuralgia, the following features of the resulting denervation were studied:

1. *Disturbance of Taste.*—According to current opinion, based on loss of taste in the anterior part of the tongue following paralysis of the facial nerve, taste sensation is carried from the anterior two thirds of the tongue by the chorda tympani nerve and is relayed to the brain stem by the nerve of Wrisberg. There is probably also a pathway through the otic ganglion to the great superficial petrosal nerve, and thence to the geniculate ganglion and the nerve of Wrisberg. Neither of these accepted pathways should be injured on section of the trigeminal nerve, yet this procedure interferes with taste sensation. Objective tests with the tongue extended showed delay in the appreciation of salt, sugar, vinegar and quinine sulfate in 12 of 20 cases within fourteen days of operation and complete loss of sensation in 6 others, taste sensation on the side of operation being normal in only 2 cases. Subjectively, all patients complained of disturbance in taste sensation. It is suggested that this disturbance of taste sensation cannot be attributed to interruption of taste-conducting fibers. It may be compared to the peculiar dysesthesias and subjective numbness which are noted in the skin of the face in cases of this procedure. If one modality of sensation is removed, then, even though the remaining modalities remain intrinsically unaltered, they will not be able to stimulate the sensorium normally. In the case in question, in taste impulses lack the background of common sensation.

2. *Innervation of the Cornea.*—Section of the maxillary division of the fifth nerve produces anesthesia which does not include the cornea. Section of the ophthalmic division produces complete anesthesia of the entire cornea. After the Sjöqvist operation, with section of the descending fibers of the trigeminal tract in the medulla, there is loss of pain sensation in the cornea, but light touch sensation is retained.

3. *Movements of the Tongue.*—Bilateral section of the trigeminal nerve causes movements of the tongue to become uncertain and irregular. This ataxia gradually improves, and it is suggested that there may be sufficient proprioceptive fibers in the hypoglossal nerve to assume the function of those cut in the trigeminal nerve.

4. *Changes Referable to the Sympathetic Nervous System.*—Vasomotor changes in the face have been reported only in cases in which nerve interruption was effected by injection of alcohol, and may have been due to spread of the alcohol to the carotid plexus. In cases of avulsion of the supraorbital nerve no evidence of vasomotor disturbance was observable several months after the operation, although the area was still entirely numb. Section of the descending tract in the medulla caused no vasomotor changes. The author concludes that sympathetic fibers are not present in the caudal parts of the trigeminal tract, and that they do not follow accurately the peripheral branches of the trigeminal nerve.

5. *Great Superficial Petrosal Nerve* (paralytic interstitial keratitis).—Section of the great superficial petrosal nerve produces a marked decrease in the secretion of the lacrimal gland on the affected side. This, however, is not sufficient to produce dryness of the eye, nor does it result in keratitis unless the cornea is also anesthetic. Analgesia of the cornea, as produced by section of the descending tract of the trigeminal nerve in the medulla, led to keratitis in 1 case. Rowbotham concludes that the primary factor is repeated trauma to the unprotected analgesic cornea, although other contributory factors cannot be excluded.

MASLAND, Philadelphia.

BLOOD-PRESSURE IN CARDIAZOL [METRAZOL] EPILEPSY. E. GUTTMANN and F. REITMANN, J. Ment. Sc. **85**:787 (July) 1939.

Guttmann and Reitmann studied the blood pressure curve during epileptic convulsions induced with metrazol. The curve of the blood pressure between the

injection of metrazol and the occurrence of a fit showed an initial rise; this was followed by a fall which coincided with the fit and, finally, a steep rise, which did not entirely subside to the initial line. Subconvulsant doses produced a rise in blood pressure, dependent in degree on the dose and the initial level. The nearer the dose to the convulsant threshold, the greater the increase of blood pressure. Keeping the blood pressure low by means of amyl nitrite prevented the occurrence of a fit. A sudden increase of blood pressure following an intravenous injection of benzedrine did not, however, produce a fit when the dose of metrazol was subliminal.

KASANIN, San Francisco.

STUDIES OF WATER METABOLISM IN ESSENTIAL EPILEPSY. G. D. GREVILLE and TUDOR S. G. JONES, J. Ment. Sc. **85**:903 (Sept.) 1939.

Greville and Jones studied the diurnal water exchange in 2 epileptic patients for approximately four months and in a third patient for one month. Similar measurements were made on 2 nonepileptic patients as controls. No certain evidence was obtained that the urinary excretion was decreased before a fit and increased afterward, as has been often claimed. The water balance was determined daily as completely as was practicable. The daily excretion of chloride in the urine under constant salt intake at two levels also failed to show any relation to the incidence of fits. Serial investigations were made of the concentration of constituents of the blood which might be affected by changes in the water content of the organism, viz., protein and nonprotein nitrogen in the plasma and hemoglobin and total solids in the whole blood. Here, again, contrary to the findings of other authors, the variations were apparently not associated with the incidence of fits.

KASANIN, San Francisco.

CREATININE IN MENTALLY DEFECTIVE PATIENTS. L. S. PENROSE and CECILIA E. M. PUGH, J. Ment. Sc. **85**:1151 (Nov.) 1939.

Penrose and Pugh made a survey of over 500 estimations in duplicate of creatinine and creatine excretion in early morning specimens of urine from nearly 300 male and 100 female mentally defective persons. The patients were purposely kept on ordinary institution diet. The results were expressed in terms of the creatinine level, the specific gravity of the sample being taken into account, and the ratio of creatine to creatinine. It was found that in muscular dystrophy the excretion of creatine is greatly increased, at the expense of that of creatinine. This holds true also for diplegia. The creatine value was found to be high for patients suffering from hyperthyroidism and relatively high for patients under thyroid therapy. High creatine and low creatinine values were observed in children.

In cerebellar ataxia and postencephalitis the creatinine excretion was high. Except for postencephalitis, psychosis with mental defect apparently was not associated with any abnormality of creatinine and creatine excretion. There appeared to be a slight increase in creatine excretion in cases of congenital syphilis. The results were normal for persons with mongolism and epilepsy. For patients with endocrine dystrophies the results were irregular and varied with the nature of the disturbance. It was further noted that: (1) slight creatinuria is normal with a diet containing probably less per day than the usual test dose of creatine, even when the estimation is made on an early morning specimen; (2) there is no significant difference between the average creatine excretion of men and of women patients; (3) owing probably to their greater average size, and consequently greater muscle bulk, the average creatinine excretion of men is greater than that of women.

KASANIN, San Francisco.

THE QUICK COMPONENT OF NYSTAGMUS. A. K. MCINTYRE, J. Physiol. **97**:8 (Nov.) 1939.

McIntyre undertook to determine whether the rhythm of nystagmus is central in origin or is dependent on afferent impulses from the ocular muscles. He took

advantage of the fact that nystagmus causes characteristic changes in the action potentials of the third, fourth and sixth cranial nerves which can be detected in the central stumps of these nerves after they are severed. Since elimination of all afferent impulses from the eye muscles by cutting all the nerves supplying the muscles did not alter the action potential characteristic of nystagmus, he concludes that the rhythm is entirely central in origin and independent of impulses from the ocular muscles.

Incidentally, he noted that the action potentials responsible for muscle tone in these muscles were unaltered by division of the nerves, proving that the ocular muscles differ from other muscles in the body in that their tone is not dependent on proprioceptive impulses from the muscles themselves.

THOMAS, Philadelphia.

EFFECT OF ACETYLCHOLINE, PROSTIGMINE, POTASSIUM AND FATIGUE ON THE CROSSED EXTENSOR REFLEX AND ON ITS REFLEX INHIBITION IN THE TOAD. CLARA TORDA, J. Physiol. **97**:357, 1940.

Torda studied the influence of acetylcholine, prostigmine, excess of potassium and fatigue on the crossed extensor reflex of the toad and on its inhibition by homolateral stimulation. A weak homolateral stimulus inhibits, but a stronger one augments, the contralateral reflex response. Increased intensity of contralateral stimulation increases the strengths of the homolateral stimuli needed to produce these effects. Both contralateral and homolateral extensor reflexes are paralyzed by acetylcholine and prostigmine in high concentrations. A relatively weak homolateral stimulus antagonizes the paralyzing effects of acetylcholine and prostigmine on the contralateral extensor reflex. This effect of the homolateral stimulus has been observed when it was applied both during and immediately preceding the contralateral stimulation. Fatigue has almost the same effect as acetylcholine or prostigmine. Potassium (four to eight times the normal content) produces no qualitative change in the reflexes.

THOMAS, Philadelphia.

VARIATIONS IN NITROGEN OF THE BLOOD AFTER CEREBRAL AND MENINGEAL HEMORRHAGES. F. RAGGI, Riforma med. **55**:1611 (Nov. 11) 1939.

Raggi followed the behavior of azotemia in 38 cases of cerebral or meningeal hemorrhage in persons who had normal kidneys and no history of renal disease. The determinations of nitrogen in the blood were made on the day the stroke occurred or two or three days after and then at intervals of three days for three weeks and of one week for one month. The author found that in all cases of cerebral and meningeal hemorrhage the amount of nitrogen in the blood increases within the first few days after the stroke occurs. Values for hyperazotemia do not exceed 1 mg. of nitrogen for each thousand cubic centimeters of blood and last no longer than a week or twelve days in cases of moderate cerebral lesion from hemorrhage. Values for hyperazotemia vary between 1.2 and 1.6 mg. of nitrogen for each thousand cubic centimeters of blood and last for two or three weeks in cases of grave hemorrhage in which there is evolution to recovery, and between 2 and 3 mg. in cases of acute conditions in which there is coma, with death three or four days after the stroke. If death occurs within one or two days after the stroke hyperazotemia does not appear. The author concludes that the variations of nitrogen in the blood in cases of cerebral and meningeal hemorrhage are of prognostic value. With the exception of the cases in which there is a rapidly fatal evolution, the more acute the cerebral lesion from the hemorrhage the more unfavorable the evolution of the condition and the higher the figures for hyperazotemia.

J. A. M. A.

RELATION OF PUPILLARY REACTIONS AND THE DIENCEPHALON. W. R. HESS, Klin. Monatsbl. f. Augenh. **103**:407 (Oct.-Dec.) 1939.

Hess employed electrical stimulation and exclusion of diencephalic areas in his studies on the effect of the diencephalon on the pupillomotor reactions. The experiments, which were made on cats, revealed that the diencephalon influences the width of the pupils. Stimulation of the diencephalic regions elicits the miotic as well as the mydriatic mechanisms. The pupillomotor effects that are elicited by way of the diencephalon are characterized by bilaterality, even if the diencephalic stimulation is unilateral. Another peculiarity of diencephalic influences on pupillomotor reactions is their coupling with other symptoms. Dilatation of the pupils is always accompanied by symptoms of excitation, whereas pupillary contraction concurs with signs of diminished activity. On differentiating electrical examination, the diencephalic action spheres, in the hypothalamus as well as in the thalamus, are separated into an anterior field, which exerts a contracting effect, and a posterior and partly laterally located field, which exerts a dilating effect. In evaluating the clinical significance of these observations, the author stresses that when central disturbances are suspected, the width of the pupils must be controlled with regard to absolute or standard illumination; that is, it has to be determined whether under standard illumination the pupil is too wide or too narrow. Furthermore, it is necessary to watch for accompanying symptoms. It must be remembered that unilateral focal symptoms cause bilateral pupillary changes when their cause is in the posterior hypothalmus and bilateral, but dissimilar, pupillary changes when their cause is in the lateral hypothalamus. In connection with the question whether experimental observations on cats permit conclusions regarding conditions in human subjects, the author states that the relatively primitive regulatory mechanisms controlled by the sympathetic nervous system have considerable uniformity throughout the entire scale of vertebrates. Nevertheless, the final decision must be based on clinical observations.

J. A. M. A.

Psychiatry and Psychopathology

CEREBRAL DAMAGE IN HYPOGLYCEMIA. A. B. BAKER, Am. J. Psychiat. **96**:109, 1939.

Baker studied the effects of hyperinsulinism as seen in insulin shock occurring in diabetic patients, in spontaneous hypoglycemia resulting from pancreatic disease and in insulin shock produced therapeutically and experimentally in animals.

In all groups the author found essentially the same pathologic changes: changes in nerve cells, cerebral petechial hemorrhages, glial proliferation and areas of demyelination. He reports 4 cases. In 1 case a diabetic patient died in insulin shock and showed the pathologic changes mentioned; in 2 cases diabetic patients went into shock after large doses of insulin and presented sequelae, such as aphasia, hemiparesis and severe mental changes, and in the fourth case a schizophrenic patient remained in prolonged insulin coma and after this was confused, misidentified people and was overactive. Baker compares the pathologic picture of insulin shock with that of cerebral anemia and concludes that the two are similar.

FORSTER, Boston.

ON SUBLIMATION. FRANCES DERI, Psychoanalyt. Quart. **8**:325, 1939.

Sublimation has been defined as the process by which an instinct becomes deflected from its original aim and original object and is gratified by acceptable social or cultural activity. Deri adds several postulates to this definition: (1) Sublimation is the result of an ego defense against pregenital impulses; (2) only such pregenital impulses as have their source in bodily organs which subserve self preservation can be sublimated; (3) pregenital impulses which are derived from and split off from functions of bodily organs yield the energy necessary for

achievement; (4) genital impulses cannot be sublimated; (5) genital impulses cannot yield energy for achievement because they subserve solely the purpose of enjoyment.

In the development of the child, every pregenital impulse is dealt with in three ways: Part of it remains as a form of fore pleasure; part of it succumbs to reaction formation and these integrated reaction formations form the character, and a large part is deflected from its original aim and object and is expressed first by play activity and later by activities of achievement. In the normal person there is maintained a division between pregenital impulses subserving self preservation and genital impulses subserving enjoyment. In the neurotic person this normal division has broken down, and attempts are made to attain end pleasure through pregenital impulses and to use genital force for self preservation. As genitality cannot be sublimated, the normal person, if he is prevented by external reasons from finding an adequate love object, can only repress his genital desires or regress to the gratification of masturbation.

Sublimations are best obtained when the pregenital impulse is given up, because the value of the genital gratification is greater than can be obtained from the gratification of the pregenital impulse. An adequate sublimation is not obtained when fear forces the renunciation of the pregenital gratification.

PEARSON, Philadelphia.

THE SOCIAL AND CULTURAL IMPLICATIONS OF INCEST AMONG THE MOHAVE INDIANS. GEORGE DEVEREUX, Psychoanalyt. Quart. **8**:510, 1939.

Devereux presents data, collected both from the legends and from the present day life of the Mohaves, regarding incest and the taboos against it. He tentatively interprets this material as follows: The libido of the Mohave child is distributed more or less uniformly over a large area of the body social, so that there is hardly any difference between the duties to the next of kin, those to the remote relatives and those to the tribe as a whole. This strong social feeling is the bond that produces tribal solidarity. In instances in which a family is stingy or in which there are incestuous attachments, the family or the couple automatically detaches itself from the give and take pattern of tribal existence; i. e., a strong object cathexis is invariably inversely proportional to a strong social feeling. This makes incest an asocial form of behavior; it is against this antisocial, uncooperative aspect that the taboo is directed.

Devereux cautiously presents the suggestion that among the Mohaves the family, not the horde, must have been the first semistable grouping of human beings, and that strongly cemented biologic families and romantic love cannot obtain social sanction except in strongly cemented societies. In our own times the family is not a social unit but a shelter from the wear and tear of social life, and the sanctity of the home seems to be essentially the sanctity of socially harmless escape mechanisms. However, among the Mohaves the family is a social unit which really grows because the emotional bonds are tenuous.

PEARSON, Philadelphia.

ON RETAINING THE SENSE OF REALITY IN STATES OF DEPERSONALIZATION. C. P. OBERNDORF, Internat. J. Psycho-Analysis **20**:137 (April) 1939.

One of the most important mechanisms in the feeling of unreality is thought repression by means of which the patient represses aspects of his superego which he considers to be harmful to himself. As a result of such repression he begins to feel that he is not the same person as formerly. In no case, however, in the author's experience, has the patient completely failed to recognize himself. Depersonalization results from the need of the patient to rescue himself from the outside world, which in his own development is bound up with one or the other parent. Such patients constantly tend to shift the conversation to inconsequential topics, and by extreme politeness protect themselves from the outside world and reenforce an impersonal relationship with other people. The feeling

of unreality may extend to parts of one's own body, as in the case of a patient who felt that his own penis was something foreign and unnatural to him. In another patient all feelings, such as rage, fear and love, seemed to be extremely unreal and nonexistent so that she rarely experienced them. On the other hand, books, writing and reading seemed to be extremely real to the patient. In other cases inanimate objects assume a realistic vividness. They become part of the patient's emotional life and assume great importance in his experiences. Analysis shows that these objects are frequently identified with parental sex organs, as in the case of a girl who called her pillow "pilpil." Analysis in this instance showed that the pillow symbolized the father's penis.

A somewhat unusual case is reported by Oberndorf in which, after two years of analysis, the patient stated that the analysis dealt with the neurotic symptoms of his secondary personality. Underneath was the original personality, in which the feeling of unreality was so strong that a secondary personality, which was in closer contact with the outside world, had developed. The secondary personality developed as a need in the patient to take his mother's place, as he felt that he was responsible for his mother's insanity.

The subject of depersonalization is still extremely obscure and needs much investigation.

KASANIN, San Francisco.

ROLE OF THE FEMALE PENIS PHANTASY IN MALE CHARACTER FORMATION. S. LORAND, Internat. J. Psycho-Analysis **20**:148 (April) 1939.

Lorand states that there are patients who in their dreams and fantasies attribute the possession of a penis to women and of a vagina to men. Certain typical behavior problems recur in the difficulties of these patients. Their attitudes toward women show sexual, and toward men social, maladjustment. They seem unable to endure frustration and use every means to avoid it by trying to make those men who are their superiors socially, in the family or at work behave leniently and indulgently toward them; that is, they try to convert them into "motherly fathers." They thus spare themselves the unendurable thought of being threatened or harshly treated.

In general, the family constellation proves to be of utmost importance in all cases of this type. The main features are an unconscious but strong attachment to the female members of the family, particularly the mother, and at the same time a repressed hostility to the father. The unconscious tendency to castrate the father is paralleled by a similar tendency to self castration as an attempt to placate the father. As these persons are hypersensitive and unable to endure frustration, their constant, if unconscious, aim is to restore the emotional atmosphere of childhood. This aim finds expression in a continual shift of identification. Having only a weakly developed character of their own, they want to be, and therefore are, like both parents at once, a phallic mother and a vaginal father.

An important factor in the development of these fantasies of a female penis is the lack of child companionship. Almost without exception the patients had had no contacts with other children during their formative years. They were usually the youngest in the family, and their only playmates were much older siblings, nursemaids or parents. Consequently, their opportunities for satisfying sexual curiosity were limited. They were unable to make comparisons with children of their own age, and the rare glimpses they could obtain of the adult genitals, whether male or female, obscured by the pubic hair, which figures largely in their fantasies, mystified rather than enlightened them.

A careful study of these cases makes it plain that the disturbance began in infancy as a result of the mother's attitude. In this infantile pregenital period the child confuses the breast with the penis. The fantasy of the mother possessing a penis reaches its height in early childhood, during which the child has definite phallic strivings toward the mother. Naturally, at this period the child also experiences marked castration anxiety in connection with the father. This is not uncommon, and if the child is met with affection rather than frustration a normal development takes place. On the other hand, if the child is continually frus-

trated, his anxieties increase with the development of a weak ego, which tolerates considerable infantile sexual fantasy. If the mother is extremely severe, the child tries to make the father into a kind mother with the extrinsic development of sexual fantasy, much as the author has described.

KASANIN, San Francisco.

AFFECTIVE SEQUELAE OF CONVULSANT DRUG THERAPY. JOHN B. DYNES, J. Ment. Sc. **85**:489 (May) 1939.

Of a series of 77 patients treated with convulsant drugs, Dynes found that in 7 there developed typical states of euphoria and elation. These affective disorders should be separated clearly from periods of excitement and confusion which frequently follow an induced convulsion and persist for from a few minutes to a few hours. The states of elation and euphoria reported by Dynes were not associated with confusion and lasted from four days to two months. The change in mood and behavior was the significant feature, and was in striking contrast to the patient's mental picture prior to the administration of the convulsant drug.

An interesting feature in this group of cases was that the majority of affective reactions appeared after one or two convulsions.

KASANIN, San Francisco.

UNDESIRABLE MENTAL SEQUELAE TO CONVULSANT DRUG THERAPY. JOHN B. DYNES, J. Ment. Sc. **85**:493 (May) 1939.

In a series of 68 patients treated with convulsant drugs, 10 presented undesirable mental sequelae in the nature of prolonged periods of violence (3 patients) or evidence of gross intellectual deterioration (7 patients). Prolonged courses of treatment, with twenty convulsions or more, have in Dynes's experience been unjustified, and in certain cases have led to undesirable sequelae. Improvement, when it occurred, was noted after from one to four convulsions. The undesirable sequelae of convulsant drug therapy which Dynes reports lend clinical confirmation to the belief that prolonged use of convulsant drugs in certain cases produces degenerative changes in the brain.

KASANIN, San Francisco.

FAMILIAL PRESENILE DEMENTIA: REPORT OF CASE WITH CLINICAL AND PATHOLOGIC FEATURES OF ALZHEIMER'S DISEASE. W. H. MCMENEMEY, C. WORSTER-DROUGHT, J FLIND and H. G. WILLIAMS, J. Neurol. & Psychiat. **2**:293 (Oct.) 1939.

McMenemey and his co-workers present a case of Alzheimer's disease with typical clinical and histologic observations. Investigation of the family history revealed the fact that 3 of 4 siblings of the previous generation, including the patient's father, suffered from presenile dementia, which in all probability was identical with that of the patient. As in the case of familial Alzheimer's disease described by Löwenberg and Waggoner, the parents of the first affected generation were cousins.

J. A. M. A.

CRIMES COMMITTED IN A STATE OF MENTAL CONFUSION. EDGAR LEROY and PIERRE MASQUIN, Encéphale **34**:169 (April) 1939.

Leroy and Masquin discuss the medicolegal aspects of crimes committed in a period of clouded consciousness followed by amnesia. They are concerned not with deliriums due to toxins or those following an epileptic seizure, but with the poorly understood confusional states in which there is not enough incoherence and motor incoordination to arouse suspicion. The authors report 3 cases in which the evidence was satisfactory that simulation did not exist. One subject was feebleminded; all 3 were emotionally unstable and sadistic and had ideas of injustice and persecution. A toxic state could not be demonstrated. The criminal

acts are apparently the result of impulses springing from unconscious conflicts. For this reason the authors attach no legal responsibility to the acts.

RHEINGOLD, Chicago.

Meninges and Blood Vessels

MENINGITIS DUE TO MICROCOCCUS TETRAGENUS. THORBURN S. MCGOWAN and PAUL KISNER, Arch. Int. Med. **64**:15 (July) 1939.

McGowan and Kisner review the 7 cases of meningitis due to Micrococcus tetragenus previously reported, to which they add 1 case of their own. They believe that realization of the inherent characteristics peculiar to M. tetragenus should result in the future in the recognition of the condition in an increasing number of patients.

The organism is a common inhabitant of the nose, throat and sputum of patients with tuberculosis. Although it has been regarded as a nonpathogenic organism, it may become invasive when the general resistance is lowered. The clinical manifestations in all the reported cases, including that of the authors, followed closely those of meningococcic meningitis. The onset was usually sudden; all the patients were in virile adult life; the duration of the illness ranged from one to five weeks. Comparison of symptoms revealed that a differential diagnosis between meningitis due to M. tetragenus and meningococcic meningitis depends on bacteriologic studies rather than on the clinical manifestations.

M. tetragenus tends to dissociate into three types of colonies: (*a*) yellow, (*b*) large and small white and (*c*) translucent. It was found that, once dissociated, each type of colony on transfer to various mediums maintains its characteristics. The micrococcus elaborates a soluble toxin which produces a cutaneous reaction in human subjects but is not demonstrably toxic for animals. Serologically the yellow colony is more nearly related to the meningococcus.

BECK, Buffalo.

SUBARACHNOID HEMORRHAGE FROM AN EPENDYMOMA ARISING IN THE FILUM TERMINALE. KENNETH H. ABBOTT, Bull. Los Angeles Neurol. Soc. **4**:127 (Sept.) 1939.

Abbott reports the case of a youth aged 16 who, after attempting a high jump, experienced sharp pains in the lumbar region and in both lower extremities. Severe headache followed, with weakness and flexor spasms of the legs. There was rigidity of the neck, with positive Kernig and Brudzinski signs, but no paralysis. The spinal fluid was bloody and under increased pressure, but there was no subarachnoid block. The patient recovered rapidly, but had over twenty-five similar attacks in the next fourteen months. In the last attack tenderness was present over the lumbar vertebrae, without sensory or motor changes. Spinal punctures became progressively more difficult and the fluid more bloody. Roentgenograms following injection of iodized poppyseed oil revealed a block at the level of the first lumbar vertebra. At operation a large encapsulated tumor, which proved to be an ependymoma with an unusual amount of hemorrhage, was removed from its attachment to the filum terminale. At autopsy the meninges were observed to be stained brown and the cerebral ventricles slightly dilated.

MACKAY, Chicago.

EXPERIMENTAL CONTRIBUTION TO EPIDURAL AND SUBDURAL HEMATOMA AND THERAPEUTIC VALUE OF DEHYDRATION AND REPEATED CISTERNAL PUNCTURE. Y. KABUKI, Arch. f. klin. Chir. **197**:230 (Oct. 12) 1939.

Kabuki observed the clinical course and the microscopic appearance of epidural and subdural hematomas which he had produced in dogs for from three to one hundred and twenty days. Organization of the hematoma of either type takes

place from the dural side several days after the operation and is completed in from fourteen to twenty days. Organization of the blood in the case of the subdural hematoma proceeds from the dura alone, without the participation of the pia or the arachnoid, whereas in the case of the epidural hematoma one finds in addition to the proliferation from the dura, endothelial cells and various cells proliferating from the bony surface. In both the subdural and the epidrural variety the author observed the formation of the membrane lined with a thin layer of cells of mesothelial type and considered by many authors to be characteristic of the subdural hematoma. With the formation of new capillaries, he had observed spaces lined with endothelial cells. These were lined in the early stages with a layer of interlacing fibers, but not with fibroblasts. The author considered these spaces as blood spaces analogous to new capillaries. Foci of calcification were observed in microscopic preparations from ten to twenty-four days old. Dehydration therapy practiced in one group of these dogs had no effect on the organization of the hematoma. In some of these animals the loss of fluid caused, in addition to shrinking of the brain tissue, alterations suggestive of beginning degeneration of the ganglion cells. Organization of the blood began sooner and was completed more promptly in the series in which repeated cisternal punctures were practiced. Among the clinical manifestations the author emphasizes conjunctival hemorrhage, which made its appearance on the first postoperative day, as a rule, and which disappeared by the seventh to the tenth day. This symptom had not been previously mentioned. The cerebrospinal fluid showed distinct differences in the two types of hematoma. In the epidural type there was only a mild increase in the cell count, and this soon returned to normal, while in the subdural type the cerebrospinal fluid was distinctly hemorrhagic. Xanthochromia and a positive Nonne-Apelt reaction were present, and the increased cell count persisted for as long as two weeks. As a rule, the animals exhibited clonic spasms, convulsions and pareses of the lower extremity of the corresponding side. Secondary bleeding was not unusual and took place as a rule between the dura and the hematoma, in 1 case thirty days after the operation. The process of organization of both types of hematoma is typical. It consists of proliferation of spindle-shaped reticulum cells which form interlacing connective tissue fibers.

J. A. M. A.

PATHOLOGIC FEATURES AND SYMPTOMS OF DIFFUSE CARCINOMATOSIS OF THE MENINGES. I. SCHEINKER, Monatschr. f. Psychiat. u. Neurol. **101**:275 (Aug.) 1939.

Scheinker reports 3 cases of carcinomatosis of the meninges. Histologic study showed that the tumor cells spread freely through the subarachnoid space and extended along the perivascular spaces of the cerebral vessels, without forming circumscribed masses or penerating the pial and glial limiting membranes. Collections of neoplastic cells were especially abundant in the subarachnoid space around the cranial nerves and spinal roots, apparently owing to mechanical factors relating to the flow of cerebrospinal fluid. According to Scheinker, meningeal carcinomatosis occurs more frequently than is suggested by reports in the literature. In most instances the correct diagnosis is not made clinically, and macroscopic examination of the nervous system may fail to disclose abnormalities. Yet the clinical picture is as a rule characteristic enough to permit one to diagnose the condition. The illness usually begins with irritative meningeal phenomena, which are soon followed by symptoms of involvement of cranial nerves or spinal roots. In a few cases lumbar puncture has provided diagnostic aid by revealing epithelial cells in the spinal fluid. It is probable that diffuse meningeal carcinomatosis results from invasion of the nervous system by way of lymph passages, whereas circumscribed cancerous tumors are probably hematogenous in origin.

ROTHSCHILD, Foxborough, Mass.

SUBARACHNOID HEMORRHAGE. K. E. PASS, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:400 (Aug.) 1939.

Pass observed 60 cases of subarachnoid hemorrhage during a period of four years. He found that aneurysms were more often the cause of such bleeding than arteriosclerosis. Thirty-five per cent of the patients were between 40 and 50 years of age. In about one-third a labile blood pressure was encountered. Persistently high blood pressures and pressures associated with arteriosclerosis were less frequent. The author mentions the probable role of hormonal factors in women. In 48 per cent of the female patients there was a definite relation of the meningeal bleeding to the menstrual periods. He emphasizes also the frequency and clinical importance of vegetative disturbances during the course of subarachnoid hemorrhage. These vegetative changes are due to injury to the hypothalamic region, since the most frequent site of bleeding is from the circle of Willis. Psychic trauma may sometimes raise the blood pressure and be the immediate cause of subarachnoid bleeding. The frequency of the Korsakoff syndrome is explained on the basis of injury to the hypothalamic region.

SAVITSKY, New York.

Diseases of the Brain

MENINGIOMA PRODUCING UNILATERAL EXOPHTHALMOS: SYNDROME OF TUMOR OF THE PTERIONAL PLAQUE ARISING FROM THE OUTER THIRD OF THE SPHENOID RIDGE. JAMES W. SMITH, Arch. Ophth. **22**:540 (Oct.) 1939.

Smith calls attention to the diagnostic syndrome of the outer third of the sphenoid ridge. The syndrome of meningioma, plaque arising from the outer third of the sphenoid ridge, consists of unilateral exophthalmos; normal eyegrounds, normal fields and normal vision; suprazygomatic fulness, and roentgen findings of hyperostosis involving the sphenoid ridge, the greater and lesser wings of the sphenoid, the roof of the orbit and the area where the frontal and parietal bones articulate with the greater wings of the sphenoid.

SPAETH, Philadelphia.

CEREBRAL COMPLICATIONS FOLLOWING SURGICAL OPERATION. ALBERT BEHREND and HELENA E. RIGGS, Arch. Surg. **40**:24 (Jan.) 1940.

Behrend and Riggs studied 21 cases of postoperative cerebral complications, special attention being given to the condition for which the operation was performed, the operative risk, the age of the patient and the type of anesthetic used. Cerebral complications following surgical operation are not rare. Such complications are seldom the result of embolism or hemorrhage. The cerebral lesion is usually diffuse, involving the entire brain. Examination of the brain and other viscera reveals that cardiocirculatory efficiency usually has been impaired long before the operation is performed. This impairment is manifested chiefly by parenchymatous edema and congestion, and by perivascular fibrosis. The presence of diminished circulatory efficiency is usually unsuspected. Any anesthetic agent may contribute to the production of postoperative cerebral complications. Cerebral complications (psychoses, coma, convulsions, paralysis) after surgical operation are frequently the sequels of relative cerebral anoxia produced by an alteration in blood pressure, occurring as a result of the effect of surgical operation and of the anesthetic on a patient with impaired cardiocirculatory efficiency.

GRANT, Philadelphia.

APOPLEXY IN EARLY LIFE. GUSTAV E. STÖRRING, Ztschr. f. d. ges. Neurol. u. Psychiat. **167**:405 (Aug.) 1939.

The word apoplexy is used to designate the sudden, apoplectiform appearance of focal cerebral signs. Störring emphasizes that there are causes other than syphilis and embolus for apoplexy in young persons. Multiple sclerosis can begin

in this way. Sudden hemorrhage into a glioma, as well as cerebral metastases from a primary carcinoma elsewhere, may account for the sudden onset of symptoms. Spontaneous subarachnoid hemorrhage and traumatic subdural hematoma are mentioned as occasional causes.

Störring emphasizes particularly the fact that functional vascular spasms, such as occur in migraine, can be the cause of softening in the brain. Fortunately, in most cases the spasm relaxes before irreparable damage is done, usually giving rise to the well known fleeting focal signs encountered in this disease. Hypertension as a cause of apoplexy in young persons is mentioned. In 1 case, that of a man aged 26, a hormonal origin of the hypertension was postulated during life, since there were abnormal fat distribution, striae and absence of evidence of renal damage. At autopsy malignant nephrosclerosis was found. The author comments on the fact that in this case a cerebral hemorrhage was observed at autopsy without a history of loss of consciousness. Hypertension is sometimes due to an adrenal tumor or to pituitary basophilism, for which roentgen treatment of the hypophysis can be given. Störring observed 4 cases of apoplexy in young persons in which no cause for the cerebral accident could be found.

SAVITSKY, New York.

ACUTE DISSEMINATED ENCEPHALOMYELITIS AND ITS EVENTUAL CONNECTION WITH POSTINFECTIOUS AND POSTVACCINAL NERVOUS COMPLICATIONS. F. MÖLLER, Nord. med. (Finska läk.-sällsk. handl.) **4**:3215 (Oct. 28) 1939.

Möller says that, especially in 1938, numerous cases of nonpurulent inflammation of the central nervous system occurred in Ångermanland, Sweden, in 48 of which treatment was given at the Military Hospital in Sollefteå and are of interest etiologically, clinically and epidemiologically. While about half of the cases in which treatment was given occurred in connection with various infectious diseases (mumps, measles, smallpox, whooping cough and zoster) and vaccination against smallpox, the others seemed to appear spontaneously. About half of the cases presented types of meningoencephalitis, encephalitis or encephalomyelitis; the remaining were classified as instances of meningitis, poliomyelitis or neuritis. All but 1 of the cases of pure meningitis originated in connection with infectious diseases and vaccination. Both poliomyelitis and parotitis were widespread in the region. An increase in the number of cases of poliomyelitis occurred during February and March, which is remarkable considering the season and the figures from Sweden generally. There were cases of encephalitic and of poliomyelitic type in the same village at about the same time. The occurrence of nervous complications connected with different infectious diseases and vaccination against smallpox simultaneously with acute inflammations in the central nervous system without evident relation to such infectious diseases supports the theory of the power of a generally spread neurotropic virus which prepares the way for postinfectious or postvaccinal encephalitis.

J. A. M. A.

Diseases of the Spinal Cord

CHRONIC HYPERTROPHIC SPINAL PACHYMENINGITIS. GEORGE WILSON, HARVEY BARTLE and JAMES S. DEAN, Am. J. M. Sc. **198**:616 (Nov.) 1939.

Wilson, Bartle and Dean review briefly some of the current opinions regarding the cause, pathologic changes, symptoms, diagnosis and treatment of hypertrophic spinal pachymeningitis. They present correlations of the clinical features in 15 cases of the disease and of the gross and microscopic pathologic lesions in 12 of these cases. The outstanding clinical features in an "ideal case" appear to be: adult life; male sex; syphilis; radicular pain; an ill defined sensory level; ataxia as the most prominent symptom of cord involvement; pyramidal and vesical symptoms; intracranial signs; signs of lower motor neuron involvement, more widespread than the apparent sensory disturbance; partial block on measurement of

the manometric spinal fluid, and certain features in studies with iodized poppy seed oil, as emphasized by Moniz. The characteristic pathologic features are: lymphocytic infiltration and fibrous hyperplasia of the dura, which may be adherent to the pia-arachnoid; compression of the spinal roots and secondary degeneration of the cord, and chronic circulatory insufficiency with resultant myelomalacia of the gray and white matter over several segments above and below the level of greatest involvement. If medical therapy fails, surgical decompression should be given serious consideration.

MICHAELS, Boston.

FLACCID PARAPLEGIA FOLLOWING DIAGNOSTIC USE OF FREI ANTIGEN. H. L. KEIM and R. F. WAKEFIELD, Arch. Dermat. & Syph. **40**:709 (Nov.) 1939.

Keim and Wakefield cite a case of flaccid paralysis which began eleven days after the intradermal diagnostic use of commercial mouse brain Frei antigen. Almost complete recovery had taken place four months later. The causative mechanism of these accidents is unknown. The authors feel that the cause must be sought not in the substances administered but in a constitutional predisposition of the person affected. The recent work on virus proteins and inapparent viruses suggests that altered virus activity might help to clarify the nature of this individual susceptibility. The theoretic explanation offered is that after a period of incubation following nonspecific trauma of the skin (such as vaccination, injection, exanthems or virus eruptions) the patient responds with an interruption of his immunity by a reactivation of inapparent or latent viruses. This state of altered activity then leads to the production of paralysis and other unexplained clinical accidents.

J. A. M. A.

ACUTE AND SUBACUTE NECROTIC MYELITIS. J. G. GREENFIELD and J. W. ALDREN TURNER, Brain **62**:227, 1939.

Greenfield and Turner describe the clinical and pathologic findings in a case of acute necrotic myelitis and in 2 cases of the subacute type. The acute form is characterized by rapid destruction of function of the spinal cord in the lumbar and sacral segments. In the course of a few days there is paralysis of the legs, usually associated with rapid loss of all forms of sensation in this area. In the course of a few weeks there are loss of sphincter control and progression of the sensory involvement upward. Owing to the rapidity of the process and its severity, the reflexes remain absent. In the case cited, sensory disturbances and paralysis had extended from the sacral area to the seventh thoracic segment when death occurred, the entire illness having lasted less than two months. In acute cases of this type the spinal fluid pressure is normal. The fluid is yellow and clots on standing, and the protein content may vary between 500 and 1,000 mg. per hundred cubic centimeters. There is slight cellular increase, polymorphonuclears predominating.

The subacute form shows gradually progressing paraplegia associated with wasting of the muscles, the latter progressing in some cases to complete flaccidity. Sphincteric disturbance occurs within six months of the onset of weakness. Sensory changes are usually late, in 1 case appearing seventeen months after the onset of weakness. There is little spontaneous pain, but pain and temperature sensations are more affected than touch sense. The spinal fluid shows a moderate increase in protein, varying between 70 and 100 mg. per hundred cubic centimeters.

Pathologically, there is lacunar degeneration of the white matter of the lumbar and sacral region of the cord; in the case of the acute form this was associated with frank necrosis in some areas. The gray matter is less severely affected than the white. There is chromatolysis of the cells of the lumbar region of the cord, particularly in the anterior columns, these changes probably being secondary to axonal degeneration. The characteristic change is observed in the small arteries of the lumbosacral region of the cord. These vessels show extensive changes. The authors believe that the degeneration of the cord is in each case secondary

to disturbance of the vascular supply. In all cases there is extensive hyaline thickening of the smaller meningeal vessels. Both the media and the intima may be affected, and the vessel may be completely occluded. The veins are greatly thickened by overgrowth of connective tissue.

It is pointed out that in cases of the chronic type there is usually antecedent evidence of preexisting vascular disease elsewhere in the body, and the opinion is expressed that the degeneration of the parenchyma of the spinal cord is secondary to similar disease of the spinal vessels. MASLAND, Philadelphia.

DOES POLIOMYELITIS AFFECT INTELLECTUAL CAPACITY? R. G. GORDON, J. A. F. ROBERTS and R. GRIFFITHS, Brit. M. J. **2**:803 (Oct. 21) 1939.

Gordon and his colleagues determined the intelligence quotients, by the Stanford-Binet scale, of 98 children from 4 to 16 years of age under treatment for acute anterior poliomyelitis or its residual effects. In some of these children the onset of the disease occurred several years before the tests were applied. The mean intelligence quotient of the group was 103.91, with a standard deviation of 15.89. In comparison with a random group of normal school children whose mean intelligence quotient was 98.8, with a standard deviation of 15.2, it is seen that the mean performance of children who are suffering or have suffered from poliomyelitis does not fall below the performance of a random group of normal children drawn from the general population. A more precise examination showed that the distribution of intelligence quotients did not show any significant departure from what would be expected on the basis of the normal curve. The result was what would be obtained from a sample of similar size drawn from the general population. Therefore it can be concluded that children who suffer from poliomyelitis give the same average results as do ordinary normal children and that the variability of the results also (their spread and range) is that of a normal group. The mean intelligence quotient of the 46 girls was 102.1 and that of the 52 boys 105.5. The difference is not statistically significant. Neither was there any association between the intelligence quotient and the age at onset of the disease, the interval between onset of the disease or the occurrence of clinically recognizable cerebral symptoms at the onset of the disease. J. A. M. A.

Peripheral and Cranial Nerves

PERIPHERAL NEURITIS DURING ADMINISTRATION OF SULFANILAMIDE. J. R. WAUH, Am. J. Syph., Gonor. & Ven. Dis. **23**:745 (Nov.) 1939.

Waugh reports a case of peripheral neuritis with foot drop occurring during treatment of gonorrhea with sulfanilamide. Only 2 other cases of peripheral neuritis and 1 of optic neuritis occurring during sulfanilamide therapy are to be found in the literature. This case, the author points out, is the only one that has occurred in his service among approximately 650 hospitalized patients who have received intensive sulfanilamide treatment for gonorrhea and other urologic conditions. J. A. M. A.

PARALYSIS OF THE THIRD CRANIAL NERVE ACCOMPANYING INCREASED INTRACRANIAL PRESSURE. CLARENCE W. OLSEN, Bull. Los Angeles Neurol. Soc. **4**:123 (Sept.) 1939.

Olsen noted right palpebral ptosis and paralysis of upward, medial and downward motion of the right eye on the second postoperative day in a woman aged 33 who had suppurative mediastinitis following thyroidectomy. There were slight bilateral papilledema and a pressure of 230 mm. of water in the cerebrospinal fluid. A few hours later the left pupil became smaller, but soon dilated slowly until it equaled that on the right. The patient died on the third day. At autopsy it was discovered that the oculomotor nerves were much distorted and flattened,

particularly on the left side, by herniation of both unci through the incisura of the tentorium and compression of the nerves against the body of the sphenoid bone. In addition, there was kinking of both nerves, due to their traction between the posterior cerebral artery and the sharp margin of the tentorium near its insertion into the posterior clinoid process. The herniation of the unci was due to cerebral edema and increased intracranial pressure. Olsen believes that pupillary changes incident to increased intracranial pressure from hematomas or other causes may be produced by these mechanisms, as previously suggested by Macewen, Kaplan and Cushing.

MACKAY, Chicago.

PROGRESSIVE INTERSTITIAL HYPERTROPHIC NEURITIS. PAUL SLOANE, J. Nerv. & Ment. Dis. **90**:429 (Oct.) 1939.

Sloane reports 2 unusual cases of hypertrophic interstitial neuritis. In the first case a Negro woman aged 53 had had acute attacks of epigastric pain with vomiting for four years and progressive weakness, numbness and pain in all her extremities for one year. The pupils were small, unequal and irregular and reacted in accommodation but not to light. There were marked weakness and atrophy in the legs and forearms, without fibrillary twitches, and with brisk tendon reflexes in the upper but not in the lower extremities. The gait was steppage in character because of foot drop and talipes equinovarus bilaterally. There was glove and stocking hypesthesia for all sensory modalities below the wrists and knees. The ulnar and popliteal nerves were palpably thickened, firm, insensitive and inexcitable to electricity. The Wassermann reactions of both the blood and the cerebrospinal fluid were negative. The systolic blood pressure was 210 and the diastolic 120 mm. of mercury. At operation for cholecystectomy a small healed gastric scar and a slightly thickened gallbladder were observed. Biopsy of a specimen of the popliteal nerve revealed proliferation of the connective tissue of the epineurium and endoneurium, as well as of the Schwann cells, and almost complete loss of myelinated fibers. The vessels showed obliterative endarteritis. Biopsy of the peroneal muscle revealed degeneration and atrophy of muscle fibers and thickening of the walls of the blood vessels. The patient died a year later, after a fracture of the femur. Autopsy revealed fibrosis of the leptomeninges, convolutional atrophy of the brain and hypertrophy of the intercostal nerves, but not of the brachial or lumbar plexuses or of the cranial nerves, except the twelfth. There were generalized circulatory stasis of the brain and spinal cord and degeneration and fibrosis of the nerve roots, sympathetic chains and cauda equina.

In the second case there were normal pupils and atrophy and fibrillation of the tongue and muscles of the shoulder girdle, with relatively intact lower extremities. Sensation was preserved except for vibration sense. This patient also had primary anemia. At necropsy the spinal and cranial nerve trunks presented a typical onion bulb appearance, which was due to a colloid or mucinous substance and not to connective tissue. There were almost complete absence of the anterior horn cells in the upper thoracic region and axonal chromatolysis in the lumbar region and in Clarke's column. The dorsal and lateral columns were unaffected. The central canal was dilated and surrounded by gliotic tissue. Sloane emphasizes the association of interstitial hypertrophic neuritis with Argyll Robertson pupils in the first case and with central gliosis of the spinal cord in the second.

MACKAY, Chicago.

SURGICAL TREATMENT OF STUBBORN NEURALGIA OF THE BLADDER. E. CRISPOLTI, Ginecologia **5**:521 (Sept.) 1939.

Continuous and persistent pain is the predominant symptom of vesical neuralgia, Crispolti says. It is associated with tenesmus and moderate dysuria. The urine is clear. The symptoms are not related to menstruation. They simulate those of appendicitis, acute abdominal conditions and diseases of the kidney or of the gall-

bladder. No anatomic lesion in or around the urinary tract may be considered responsible for the condition, which is due to neuritis of the pelvicoabdominal sympathetic plexus. The author points out the utility of Cotte's operation, as modified by Pieri, in treatment of the condition. The modified operation consists in removing the upper hypogastric plexus and making an exeresis of the lateral sympathetic chains of the first sacral segment. The author reports satisfactory results from the modified operation in 2 cases. The condition dated back several years in each case. The patients were in a general nervous state. They had had various operations because of erroneous diagnoses (appendectomy and nephropexy). Removal of the upper hypogastric plexus and exeresis of the lateral sympathetic chains of the first sacral segment were followed in both cases by immediate and complete disappearance of pain and of all symptoms, control of the dysfunction of the bladder and disappearance of the nervous condition. The satisfactory results have lasted in the 2 cases up to the present (almost one year after the operation).

J. A. M. A.

Treatment, Neurosurgery

METRAZOL CONVULSIVE SHOCK THERAPY IN AFFECTIVE PSYCHOSES. A. E. BENNETT, Am. J. M. Sc. **198**:695 (Dec.) 1939.

Bennett found after convulsive shock therapy that 28 (45 per cent) of 61 depressed patients had obtained a full remission lasting from three to eighteen months and 32 (52 per cent) a social recovery, and that only 7 (11 per cent) had a relapse. Fifty-seven (90 per cent) of the 61 patients obtained rapid improvement, with termination of the depression, from metrazol shock therapy. Over 50 per cent of these patients were more than 45 years of age. Four (44 per cent) of 9 patients with a manic state obtained a full remission lasting from three to eighteen months; 4 (44 per cent) obtained a social remission, but 2 had a relapse. The average number of shocks, given every two to three days, for patients with depressive states was six to seven, with an average period of three weeks under treatment; the average number of treatments for manic patients with manic states was four, the average duration of treatment being sixteen and one-half days. Fractures of the spine and lower extremities are common complications. These can be prevented by administration of a spinal anesthetic prior to shock therapy. Convulsive shock therapy should be given only in well equipped psychiatric departments.

MICHAELS, Boston.

RESULTS AND OBSERVATIONS ON THE INSULIN SHOCK TREATMENT OF SCHIZOPHRENIA. E. D. BOND, J. HUGHES and J. A. FLAHERTY, Am. J. Psychiat. **96**:317, 1939.

Bond, Hughes and Flaherty report the results of treating 82 schizophrenic patients with insulin shock. The average period of treatment was forty-four and three-tenths days, with one hundred and six hours of stupor and two hours of coma. There was less than one convulsion per patient. The authors found that 38 per cent of the patients were recovered or much improved and maintained this status for at least eight months; 5 per cent were improved, and 29 per cent were unimproved. The highest percentage of patients who maintained their recovery after a two year interval was 28 per cent. Patients who were ill less than a year had a higher rate of recovery and maintained their recovery better than patients ill more than a year.

The authors compare the rate of recovery with insulin with the rate of spontaneous recovery at the same institution and find a spontaneous rate of 10 to 20 per cent. They comment that insight is not as prominent in patients with spontaneous recovery.

Both experimentally and clinically the authors noted a greatly prolonged negative after-potential during insulin shock and deduced that insulin causes prolonged supernormal excitability.

FORSTER, Boston.

SODIUM AMYTAL AS A PROGNOSTIC AID IN INSULIN AND METRAZOL SHOCK THERAPY OF MENTAL PATIENTS. M. M. HARRIS, W. A. HORWITZ and E. A. MILCH, Am. J. Psychiat. **96**:327, 1939.

Harris, Horwitz and Milch compared the transient effect of intravenous injection of sodium amytal with the effect two months after shock therapy. They found that 77 per cent of a group of 30 patients responded favorably to both, whereas 64 per cent of a group of 25 patients failed to respond to either insulin or sodium amytal. After administration of insulin 10 of this group received metrazol without effect. Four of the 10 had responded to sodium amytal.

FORSTER, Boston.

SULFANILAMIDE AND MENINGITIS. S. W. SAPPINGTON and G. O. FAVORITE, Ann. Int. Med. **13**:576 (Oct.) 1939.

Sappington and Favorite present 22 cases of various types of meningitis treated with sulfanilamide and review the 205 cases reported in the literature. The matter is viewed almost solely as a clinical experiment analogous to experimental work in animals in which the death or survival of the animal is the criterion of the success or failure of the therapy. This is feasible because of the almost certain fatal outcome of all forms of acute meningitis, so that recovery under treatment with sulfanilamide of any large group of patients may be reasonably attributed to the drug (except in cases of meningococcic and gonococcic meningitis, in which recovery does occur at times and the therapeutic value of the drug must be correspondingly modified). No definite conclusions can be drawn as to the value of sulfanilamide in treatment of meningitis as an entity owing to the variation in results in the different types of meningeal infection. Final opinions cannot be given in most instances until the reports of more cases accumulate in the literature. However, it may be said that the value of sulfanilamide in cases of beta hemolytic streptococcic meningitis has been established beyond dispute. A reduction of the mortality from 95 per cent and above to about 20 per cent speaks for itself. Instances of infections due to Streptococcus viridans, the tubercle bacillus or the gonococcus treated with sulfanilamide are too few for appraisal. The results so far in treatment of influenzal meningeal infections are discouraging. In cases of pneumococcic meningitis, with its terrific mortality, the outcome, 9 recoveries in 39 cases, at least warrants further trial and offers possibilities. There were 11 deaths in 84 cases of meningococcic meningitis, a mortality of only 13 per cent, which appears remarkable. However, Hoyne reports a mortality of only 16 per cent for serum-treated patients, and as many of the patients given the drug also received serum, conclusions should be withheld. However, if results are similar, sulfanilamide seems preferable. The necessity for specific serums in addition to the drug, as suggested by experimental work, has yet to be proved. As satisfactory concentrations of the drug in the blood and spinal fluid are easily attained by the oral route, it may be better to do away with intrathecal treatment and avoid the possible irritating influence of spinal taps for purposes of drainage and injection.

J. A. M. A.

Special Senses

CHANGES IN ANGIOSCOTOMAS ASSOCIATED WITH THE ADMINISTRATION OF SULFANILAMIDE. CHARLES M. ROSENTHAL, Arch. Ophth. **22**:73 (July) 1939.

Evans and his co-workers have repeatedly called attention to the widening of normal angioscotomas, as seen in cases of glaucoma, venous obstructions, retinal edema and increased intracranial pressure. They recently reported the effect of sulfanilamide on trachomatous pannus, and the known relation of sulfanilamide to the oxygen-carrying substance of the blood and hemoglobin seemed to indicate that a study of the relation of sulfanilamide to angioscotomas might be fruitful. Two subjects were selected for this study. Premedication controls were carried out. This

was followed by the administration of 15 grains (0.97 Gm.) of sulfanilamide by mouth every four hours until a total of 135 grains (8.1 Gm.) had been given. The administration of sulfanilamide was then stopped; further field charts were worked out, and, ninety-six hours later, a final control map was made in each instance. The fundi, vision and pupils showed no changes. The blood pressure remained constant throughout. Deprivation of oxygen was not studied, owing to inadequate facilities. Although in the first case there was no modification of the scotomas when oxygen was administered, during the administration of sulfanilamide there occurred narrowing of the angioscotomas; four to five days after withdrawal of the sulfanilamide the angioscotomas had returned to normal.

SPAETH, Philadelphia.

CHANGES IN ANGIOSCOTOMAS ASSOCIATED WITH INHALATION OF OXYGEN. CHARLES M. ROSENTHAL, Arch. Ophth. **22**:385 (Sept.) 1939.

Evans and McFarland, in 1938, showed that a relationship exists between oxygen deprivation and angioscotomas. They expressed the belief that the changes which they found arose from relative anoxemia at the synapses of the first and the second retinal neurons. Since the method of angioscotometry appeared to be such a delicate measure of the effects of oxygen deprivation, the test suggested itself as a method of determining the effects of increased oxygen tension. Fifteen normal persons were used as subjects. They were all unfamiliar with the possible effects of excess oxygen on the scotomas, any possible opportunities for suggestion being thus eliminated. A special oxygen mask was used, the flow of oxygen being maintained at 10 liters per minute, which gave an oxygen concentration of about 100 per cent. During the latter part of the experiment final control maps were made after withdrawal of the oxygen. The experiment showed that there was narrowing of the angioscotomas during the period of oxygen inhalation and that after the withdrawal of the oxygen widening of the angioscotoma occurred which was in excess of the amount shown by the first control charts. It seems probable from the results obtained thus far that the narrowing of the angioscotomas resulted from an increase in the oxygen content of the retina, rather than elsewhere in the visual pathway. This was evident from the pattern of the narrowing, which closely followed that of the retinal vessels. Increased oxygen content of the visual pathway, or cerebral cortex, could not result in such changes. No definite conclusions can be drawn concerning which part of the reitna was involved, although it would seem that the locus of effect was in the retinal synapse.

SPAETH, Philadelphia.

RELATIONSHIP BETWEEN PROGRESSIVE FAMILIAL MACULAR DEGENERATION AND PIGMENTARY DEGENERATION OF THE RETINA. R. MUROMATO, Ann. d'ocul. **176**:323 (April) 1939.

Bilateral primary degeneration of the retina was present in 3 brothers and sisters whose parents were second cousins. On clinical examination, 2 of them presented progressive familial degeneration of Stargardt. An ophthalmoscopic examination of the fundi and a functional experiment carried out on the third patient revealed symptoms of pigmentary degeneration of the retina. It was not possible to determine whether the changes in the fundi were caused by diffuse progressive macular degeneration which was gradually spreading or whether they extended throughout the retina at the onset. According to Muromato, progressive macular degeneration of Stargardt and pigmentary degeneration of the retina had caused primary degeneration of the external layer of the retina. Muromato believes that these two diseases are closely associated, but that the localization of the retinal degeneration varies.

BERENS, New York.

Cerebellum and Brain Stem

THE SYNDROME OF VESTIBULAR PARALYSIS IN MAN. PAUL M. LEVIN, J. Nerv. & Ment. Dis. **89**:335 (March) 1939.

The vestibule serves to initiate reflexes for righting and maintaining posture and for the ocular movements which compensate for movements of the head. Loss of these reflexes therefore produces a staggering gait and inability to right the body when it is dropped or placed in water. In addition, ocular fixation is not maintained during movements of the head. Levin illustrates this syndrome with the case of a man who began, at the age of 19, to stagger in the dark, a symptom which grew progressively worse until he fell even in the light. A year later he lost his sense of direction in the dark or when swimming under water with his eyes closed. Two years later movements of his head caused objects about him to seem to jump. There had never been any vertigo or deafness. Neurologic examination at the age of 27 showed an ataxic gait, especially with the eyes closed, and a strongly positive Romberg sign. There was no response to the caloric vestibular tests, but a normal response of the eyes to galvanic stimuli over the ears was elicited. There was no nystagmus and no adiadokokinesia, tremor or past pointing. There was no ataxia in movements of the extremities. The remainder of the neurologic examination gave normal results, as did all laboratory tests, including those on the cerebrospinal fluid. Levin believes that this patient presented in full the syndrome of vestibular paralysis, due apparently to selective degeneration of the vestibular apparatus, but seemingly not of the vestibular nerve.

MACKAY, Chicago

CENTRAL VESTIBULAR SYMPTOMS FOLLOWING DIPHTHERITIC ANGINA. R. MAYOUX, Rev. d'oto-neuro-opht. **17**:426 (June) 1939.

Four days after an attack of diphtheria there occurred paralysis of the palate, limbs and accommodation, accompanied by slight vertigo. The vertiginous sensations continued and were increased by movements of the head, especially inclination to the right. There followed incoordination of the limbs on the right side, disturbance of deep sensibility, paralysis of the right external rectus muscle and the right twelfth nerve and spontaneous nystagmus on looking to the right, sometimes becoming pendular. There was marked disturbance of equilibrium. A caloric test revealed normal nystagmus but no vertigo.

This observation demonstrates the possibility of the existence of central lesions in the course of diphtheria. The homolateral character of the disturbance of deep sensibility indicated the presence of a low bulbar lesion. Usually, vasodilatation caused by the toxin of diphtheria is transitory, but when the intoxication is intense hemorrhagic suffusions, or even true hemorrhages, in the sheaths of the vessels are produced. This probably occurred in the present case and explains the persistence of the symptoms for seven years.

DENNIS, San Diego, Calif.

DIFFUSE ANGIOMATOSIS OF THE MEDULLA OBLONGATA AND SPINAL CORD WITH CENTRAL GLIOSIS, SYRINGOMYELIA, CYST OF THE PANCREAS, RENAL CYSTS AND CYSTIC HYPERNEPHROID TUMORS OF BOTH KIDNEYS (LINDAU SYNDROME). E. KÖNIG and H. SCHOEN, Beitr. z. klin. Chir. **170**:239 (Sept. 28) 1939.

König and Schoen report a case in which a man aged 27, in the course of an illness of ten years' duration, exhibited signs and symptoms of organic disease of the central nervous system. Death was apparently due to involvement of the structures of the posterior part of the occipital fossa. Necropsy revealed extensive angiomatosis of the medulla oblongata and of the spinal cord, involving predominantly the dorsolateral aspect of the latter. There were likewise central gliosis and syringomyelia. Necropsy further revealed a cyst of the pancreas, cysts of both kidneys and bilateral hypernephromas. The authors interpreted these lesions as a result of a dysontogenic disturbance and their case as a typical example of a

syndrome described by Lindau in 1926 and known since in the literature as the Lindau, or Hippel-Lindau, syndrome. The syndrome is not limited to the developmental disturbances of the mesodermal layer of the nervous system but may exhibit, as in this case, developmental defects of the ectodermal layer as well. A hereditary tendency had been noted by several authors. The patient's family exhibited distinct hereditary lesions.

J. A. M. A.

Diseases of Skull and Vertebrae

EPIDURAL HEMANGIOMA ASSOCIATED WITH HEMANGIOMA OF THE VERTEBRAE. ROLLA G. KARSHNER, CARL W. RAND and DAVID L. REEVES, Arch. Surg. **39**:942 (Dec.) 1939.

Hemangiomas of the vertebral column are not so much a pathologic as a clinical rarity. The case reported is the twelfth in which such a condition caused compression myelitis, the first in which it was diagnosed preoperatively and the third in which it was successfully treated by operation. It is also one of the exceptional cases of vertebral hemangiomas associated with epidural hemangioma, the eighteenth case of epidural hemangioma of the spinal cord reported and the eleventh case in which the patient was cured after a laminectomy. Peculiarly, it is also the fourth case of hemangiomatous nevi of the skin occurring in the same dorsal segments as the epidural hemangiomas. Whether vertebral and epidural hemangiomas represent neoplasms or vascular malformations remains a question. They are different from hemangioblastomas and are relatively benign, slow in growth and not metastatic. Most of the accumulating evidence suggests a congenital origin. With segmental involvement of the central nervous system, cutaneous nevi are diagnostically important. As has been emphasized by Bucy and others, roentgenograms of the vertebrae reveal diagnostic peculiarities when the bone is involved by hemangiomas, particularly parallel striations in the vertebral bodies and loss of the normal homogeneous bony structure. The high percentage of deaths following laminectomy in these cases shows that the procedure is a hazardous one, and preparations for the treatment of shock and hemorrhage should be made. It is suggested that the high mortality may have been the result of unnecessarily enthusiastic surgical efforts. Although high voltage roentgen ray therapy is recommended as a postoperative measure, it would seem inadequate and hazardous to use such treatment alone when there is compression myelitis, for irreparable damage to the cord may occur before any beneficial effect can be anticipated.

GRANT, Philadelphia.

PROTRUDED INTERVERTEBRAL DISK. GILBERT C. ANDERSON and ERWIN WEXBERG, Arch. Surg. **39**:952 (Dec.) 1939.

Anderson and Wexberg report a case in which protrusion of the fourth intervertebral disk, with consecutive circumscribed spinal meningitis, gave rise to symptoms simulating those of a tumor of the cauda equina. Incision of the meningitic cyst and excision of the small protruding disk initiated recovery. This case and a few similar cases recorded in the literature suggest that a distinction is justified between (*a*) cases of lumbar or sciatic radiculitis caused by the pressure of a protruding intervertebral disk and (*b*) cases of compression of the cauda equina by a meningitic cyst which has developed from the mechanical irritation produced by the protrusion of an intervertebral disk.

GRANT, Philadelphia.

VASCULAR ANOMALIES OF UPPER LIMBS ASSOCIATED WITH CERVICAL RIBS. R. M. HILL, Brit. J. Surg. **27**:100 (July) 1939.

Hill cites a case of bilateral cervical ribs accompanied only by vasomotor disturbances of the hands of the acrocyanotic type in which removal of a rib and the fibromuscular band relieved pain, diminished swelling and improved the color of

the hand on the corresponding side. Other anatomic variations are worthy of consideration in cases of vascular disorders of the upper extremities, and with rational indications exploratory operation in this region would be warranted.

J. A. M. A.

VERTEBRAL FRACTURE IN METRAZOL SHOCK TREATMENT. H. H. DEDICHEN, Norsk med. (Norsk. mag. f. lægevidensk.) **3**:2101 (July 8) 1939.

Dedichen says that while fractures, usually of the neck of the femur, but also of the scapula and the pelvis, have been described in connection with metrazol shock, he has found the report of but 1 instance of compression fracture of the vertebral column due to this treatment. In a short time he has observed such fractures, some grave, in 6 of 80 patients treated in his hospital, and similar fractures have been noted in other hospitals since attention has been called to them. These fractures do not occur in epileptic seizures because the tonic stage is not so long and violent as in the metrazol attacks; the injury occurs during the tonic stage. The fractures resemble those seen in tetanus. The anterior part of the vertebra is almost always compressed, without injury to the spinal cord, and the posterior part remains intact. There is slight gibbus. The fracture usually occurs between the third and the ninth thoracic vertebra, where kyphosis is most marked. The author now avoids these fractures by placing a firmly folded blanket under the region of the scapula, removing the pillow and having the patient stretched full length during the metrazol seizures, not allowing him to double himself up during the attacks. The most exposed anterior parts of the vertebrae are thus kept apart, and the stronger posterior parts receive most of the pressure.

J. A. M. A.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF NEUROLOGY AND PSYCHIATRY, AND NEW YORK NEUROLOGICAL SOCIETY

LEWIS D. STEVENSON, M.D., *Chairman of the Section, in the Chair*

Joint Meeting, Nov. 14, 1939

Spastic Pseudosclerosis: Cases of Familial and Nonfamilial Incidence; A Clinicopathologic Study. DR. CHARLES DAVISON and DR. ABRAHAM M. RABINER.

This article will be published in full in a future issue of the ARCHIVES.

Epilepsy. DR. OTTO MARBURG.

After a review of changes seen in an exposed human brain during epileptic seizures, previously reported (*Arch. f. klin. Chir.* **113**:1, 1919), three factors in the production of attacks were discussed: (1) vasomotor changes—blanching of the brain (Foster Kennedy), assumed to be only a facilitating cause of seizures; (2) entrance of spinal fluid into the interarachnoid spaces (Temple Fay), an interesting, but chiefly secondary, factor, and (3) tumefaction of the brain. Contrary to the opinion of many, this tumefaction is important, and it is to the merit of Temple Fay to have put consideration of the water balance in the center of all discussions on epilepsy. In my first paper, I compared this tumefaction with the swelling of the brain described by Reichardt; this implies that water is adsorbed into the brain tissue, not into the interstices. Such adsorption is possible only through an increase of permeability, as Spiegel and Spiegel-Adolf and Prados y Such proved in cases of epilepsy by means of an exact method. In 1935 I concluded that epileptic attacks are due to an acute disturbance of water balance, caused by an increase in permeability of the blood-brain barrier and the cell membranes, with an accompanying change in salt and sugar metabolism. Many other factors must be considered. First, one must explain why a pure hypotonic solution of sodium chloride, which usually produces hydration, does not increase the readiness to thujone convulsions (Keith). This finding is opposed to the observation of Elsberg and Pike that there is an increased tendency to seizures in cases of absinth intoxication after injection of distilled water.

One finds likewise in hypoglycemic states that in certain phases there are seizures and in others none, in spite of tumefaction; Turner explained this by the difference in the glycogen content of the liver alone. Retention of sodium chloride in the liver is also well known; perhaps a change in the liver content is applicable to sodium chloride as well as to sugar, and when the sodium chloride content of the liver is high enough, hypotonic solutions of the salt are ineffective. In any case, tumefaction is an important factor in the genesis of epilepsy. It is known also that the lipoid content influences the permeability; cholesterol increases and lecithin decreases it, as recently proved by Air and Gurshot. The cholesterol content of the blood is known to drop before attacks, in a manner similar to that of magnesium. The sodium chloride-calcium and the potassium-magnesium ratios are shifted, the latter ratio toward the potassium side (Hirschfelder and Haury). In summing up, one finds that water, sugar, mineral, lipoid and albuminoid metabolisms, as well as the permeability of the blood-brain barrier and the cell membranes, are altered in epilepsy. These are all definite conditions preliminary to the attacks, and one must treat epilepsy by fighting one of these factors.

Hence, I treated epilepsy with roentgen rays, knowing that small doses decrease the permeability. The results were not completely satisfactory, but in nearly 50 per cent of cases there was success. Then I supported this treatment with preparations of the pineal gland, e. g., "epiglandol," because this gland dehydrates. I tried preparations of magnesium to increase the dehydration, to change the shift of minerals and perhaps to influence the "convulsion centers." Because 90 per cent of magnesium chloride or magnesium sulfate (Thums, Fay and others) is excreted in the feces and urine, I tried magnesium gluconate, which is resorbed better. While in one group of animals the seizures stopped after intramuscular injections, in others milder or abortive attacks occurred. Since slight acidosis increases the effect of magnesium, I also injected dextrose, after which the seizures ceased. In man I have applied magnesium gluconate only together with a barbituric preparation (best of which seems to be sodium diphenylhydantoinate, introduced by Meritt and Putnam [dilantin sodium N.N.R.]).

The paper will be published in full at a later date in the *Journal of Nervous and Mental Diseases.*

Relation of Syphilitic Optic Atrophy and Papilledema to Adhesions at the Chiasm: Indications for and Results of Surgical Treatment. DR. LOUIS HAUSMAN.

The following series of cases is presented to emphasize the need for keeping in mind the occurrence of arachnoid adhesions around the chiasm in cases of syphilis, as well as to point out the indication for surgical intervention in these cases and the benefits of this procedure in the restoration or improvement of vision.

In the neurologic service of Dr. Foster Kennedy at Bellevue Hospital, my associates and I have studied recently 15 cases of syphilitic optic disorders. In all there were a history or serologic evidence of syphilis and rapid loss of vision, frequently terminating in blindness. The ophthalmoscopic picture was of interest. In 1 case there was papilledema; in another, secondary optic atrophy, and in the remaining 13, primary optic atrophy.

Of these cases, operation was performed in 5, in 4 of which the region of the chiasm was explored. In the remaining cases the patients either refused operation or are still under observation. Only the cases will be discussed in which operation was performed. These may be divided into three groups, according to the essential clinical features.

Group 1.—The clinical picture was characterized by bilateral primary optic atrophy; heteronymous visual defects, when the patient was not totally blind; a normal ventricular system, and no evidence of increased intracranial pressure. Adhesions were present around the optic chiasm and nerves in all 3 cases.

The usual transfrontal approach to the chiasm was employed. After removal of the adhesions vision improved. The first patient in this group has now been under observation for more than two years. Before operation this patient was blind in the left eye and had temporal hemianopia in the right eye. The visual fields and visual acuity in both eyes have continued to improve steadily since the operation. Now, more than two years later, the visual fields in both eyes are greatly expanded, and visual acuity without correction is 16/15 in the left eye and 16/15—2 in the right eye. Color vision also has returned.

Group 2.—The clinical picture was characterized by secondary optic atrophy and internal hydrocephalus. No unusual adhesions were observed around the chiasm. This group is represented by case 4.

The patient gave a history of progressive loss of vision for three years. At one time she had bilateral papilledema. On admission the visual fields showed irregular concentric constriction, partly sector shaped; there was bilateral secondary optic atrophy. An encephalogram revealed internal hydrocephalus. Operation was not advised in this case because it was believed that the visual disturbances were

secondary to the internal hydrocephalus, and not to adhesions at the chiasm. However, the patient wished to have the operation, for she hoped that at least it would prevent blindness, if it did not improve vision. Operation was performed, but no unusual adhesions were seen at the chiasm; the chiasmal cistern was dilated.

Group 3.—The picture was characterized by papilledema without internal hydrocephalus. Adhesions were present around the optic chiasm. This group is represented by case 5.

The patient presented concentric constriction of the visual fields, enlargement of the blindspot and bilateral papilledema; the spinal fluid pressure was not increased. A ventriculogram did not reveal internal hydrocephalus, but diclosed slight shifting of the ventricular system to the left. Right subtemporal decompression was performed; however, the patient's condition steadily became worse. Autopsy revealed syphilitic plastic meningitis around the optic chiasm and a small gumma of the right parietal lobe.

In this case removal of the gumma in the right parietal lobe would probably not have improved visual function, for the impairment of vision was due apparently not to increase in the intracranial pressure but to exudate at the base, which enveloped and strangled the optic nerves and produced swelling of the disks through some local mechanism.

Summary.—In cases of the type of group 1, adhesions around the optic chiasm and nerves should be suspected and treated surgically. In cases of the type of group 2, it would seem that exploration of the chiasm is not indicated. The findings in group 3 indicate that in cases of this type exploration of the chiasm is warranted.

I realize that this is too small a series on which to base definite conclusions; for that reason, I am merely presenting the facts, with the hope that more cases may be studied along similar lines in an attempt to evaluate the benefit from the surgical approach which the material thus far suggests.

DISCUSSION

DR. BERNARD SACHS: I am pleased to be present at a discussion of syphilitic arachnoiditis at this day, as I was much interested in it forty years ago; it is a satisfaction to note that study of it has led to successful surgical intervention. Dr. Hausman's presentation is important for many reasons. Syphilitic arachnoiditis, as I became acquainted with it in the old days, largely through postmortem studies, was not as a rule confined to the chiasm but was an arachnoiditis which involved all the structures at the base of the brain; the great difference between the cases I have in mind and those to which Dr. Hausman has referred this evening is that in the former the visual symptoms were often associated with palsies pointing to other nerves at the base of the brain—in many cases the sixth and third nerves. I do not wish to give the impression that I instigated this investigation. Dr. Hausman, who six months or more ago told me that he was studying this problem, was himself surprised, on looking up the literature, to find that I had written on the subject forty years ago. The great advance lies in the fact that no one at that time would have dreamed of suggesting an operation for a serious syphilitic condition, such as chiasmal adhesions; the experience which Dr. Hausman has had, even though the cases are relatively few, shows the remarkable progress that has been made. From the excellent results he obtained in 3 or 4 of the cases, I think that operation should be considered whenever the probability of basal arachnoiditis is suggested, particularly if it is chiasmal.

I do not know how numerous cases of this kind will be. I have an idea they will become fewer, for those who have an experience extending over several decades know that with the improved treatment of syphilis, especially in the early stages, these serious conditions at the base of the brain are becoming less frequent, just as all know that dementia paralytica and tabes are far less common than they used to be.

I am glad to know that Dr. Hausman will continue to study this question carefully, especially with reference to therapeutic gains.

Dr. Foster Kennedy: There is little to add to what has been said, for it is a clear statement—a statement which has emerged from hard work and direct thinking. In all the cases which Dr. Hausman has described, there was no doubt a syphilitic condition at the base of the brain, but the clinical pictures certainly differed. In the second group, in which there was hydrocephalus, the operation was not indicated, because there were no chiasmatic adhesions; this group really has little to do with the first and third groups. In the second group, as Dr. Hausman pointed out, the clinical picture was characterized by production of secondary hydrocephalus through interference with ventricular drainage, and it will be noted that the blindness was not remedied. Dr. Hausman said operation was not indicated. He is right. An operation for chiasmatic adhesions which are not present is not indicated. I am not so sure that an opening into the third ventricle is not called for, because in such cases there is considerable hydrocephalus. What causes the blindness in these cases? I am sure, as will have been noted in the ventriculogram, that the third ventricle was large, far larger proportionately than the lateral ventricles. It will be noted from the history that the blindness came on in episodes with remissions, followed by total blindness. What was happening? Ventricular drainage was not effective. There was dilatation of the ventricle; then there was release of circulation, followed by subsidence of the dilated ventricle and a remission; finally, however, events led to a permanent dilatation. In each enlargement of the ventricle the floor of the third ventricle became hard and convex and was jammed down on the chiasm with considerable force; as soon as this occurred, the patient became blind. There was resolution at first, and recovery from the blindness, but finally the pressure of the floor of the third ventricle on the chiasm caused blindness, just as the adhesions in groups 1 and 3, binding themselves around the optic nerves and the chiasm, produced by direct constriction interference with sight. I believe that in the second group of cases a surgical approach is indicated, in that the third ventricle can be thrown into the general subarachnoid space, as has been done in the treatment of other forms of hydrocephalus. The pathologic basis of this condition is interesting from the point of view of what lies behind the optic atrophy of tabes. Tabes, as Dr. Sachs said, is a rare disease. One has trouble in finding tabetic patients to show to students, thanks to the genius of Ehrlich, and Dr. Hausman is dealing with an almost vestigial remnant of medicine! The shooting pains of tabes are undoubtedly due to wrapping of arachnoid adhesions around the posterior spinal nerve roots—a condition which is not really pachymeningitis, but arachnoiditis, and the same cause lies behind the optic atrophy of tabes. The disease is not a parenchymatous degeneration of the optic nerves, but a secondary result.

Dr. Sachs said that no one, forty years ago, would have thought of dealing surgically with syphilis. I do not know about that; twenty years ago it was being taught in London, by Victor Horsley, that gummas are tumors. Cerebral gummas are tumors and must be dealt with surgically. Operation on known syphilitic lesions of the nervous system was so frequently performed that one became familiar with the vital pathologic features of these conditions, and aware of such localized processes as arachnoiditis, inflammatory processes and highly focalized conditions, for example, those seen on one side of the cauda equina or in the cerebellopontile angle. Syphilis apparently picks out sunken places for attack: the peduncular space, the angle between the pons and the cerebellum, the pits made by the roots of the cauda equina—these are favored places and are susceptible to operative attack.

Dr. Abraham Kaplan: I wish to add my appreciation of Dr. Hausman's excellent presentation, and offer a sidelight on some of the cases. The first case, in which there was prompt and gratifying restoration of vision, was thought by neurologists to be one of basilar syphilitic meningitis; the neurosurgeons, in spite of the 4 plus Wassermann reaction, thought the lesion might be a suprasellar

neoplasm. During the exploration dense adhesions were encountered and freed. The benefit that followed was out of proportion to what might have been anticipated. This led to exploration in other cases.

Operation has been performed in 5 cases, in 1 of which Dr. Hausman has not as yet reported the results. Of the 5 operations, Dr. J. E. J. King performed 1, Dr. W. D. Wingebach 1, and I the other 3. There has been no fatality. Definite improvement was noted in 4 of the 5 cases.

I believe that the best explanation of the process was suggested by Dr. Sachs and Dr. Kennedy. In these cases there was a vestige of basilar arachnoiditis, early antisyphilitic treatment having made it possible for the less vulnerable cranial nerves to escape. In practically all cases there were loculi of fluid around the interpeduncular space and the chiasm; periodic accumulations and loculations of fluid in this region can conceivably cause sufficient pressure on the chiasm and optic nerves to produce optic atrophy and progressive failure of vision.

DR. J. LAWRENCE POOL: I wish to commend those who have carried out the procedure on the success. I have seen the result in some of these cases, and it has been striking. It is of interest that one should not be discouraged by the lack of immediate improvement in the field of vision. It may be two or three months before improvement occurs; this is comparable with what one sees after arachnoid adhesions of the spinal cord are freed. It remains to be discovered whether the improvement in vision is the result of removing constriction and therefore of effecting better circulation to the nerves or whether it is a result merely of removing direct pressure on nerve fibers.

DR. LOUIS HAUSMAN: I am indebted to Dr. Sachs, Dr. Kennedy and the other discussants for their comments. The point which Dr. Sachs mentioned with respect to involvement of other cranial nerves is unquestionably a great aid in the diagnosis of exudate at the base. In case 1 the olfactory, as well as the optic, nerves were involved; it was not difficult, therefore, to postulate meningitis at the base of the brain, involving these nerves. The diagnosis of syphilitic chiasmal arachnoiditis should be considered when, in addition to the picture of visual defect, optic atrophy and syphilis, there is evidence of involvement of other cranial nerves.

I think one is unduly optimistic in stating that this type of syphilitic lesion may soon disappear. I should like to mention the statistical study made by Berens and Goldberg on 100,000 cases of blindness in various institutions in New York. In reading their report I was shocked to learn in how many cases the blindness was due to syphilis, although unsuspected, and in how many there was primary optic atrophy. Berens and Goldberg found that approximately 6 per cent, or 6,000, of the patients had ocular lesions which clinically might be attributed to syphilis. Of this group only 37.5 per cent were given a serologic test for syphilis, and of this number 19.9 per cent were found to have positive Wassermann reactions. Furthermore, in the group of 6,000 patients with possible syphilitic involvement, 569 had optic atrophy. Only 50 per cent of these patients were given the Wassermann test, and 25 per cent of those tested had positive reactions (Berens, C., and Goldberg, Jacob A.: Syphilis in Relation to the Prevention of Blindness, *J. A. M. A.* **109**:777-781 [Sept. 4] 1937). It may well be that many of the cases of blindness with evidence of primary optic atrophy and serologic indications of syphilis may fall into the group of syphilitic arachnoiditis of the optic chiasm, in which surgical intervention is indicated.

I think Dr. Kennedy's criticism of group 2 is pertinent. When I described case 4 in this group and stated that operation was not indicated, I meant so far as exploration of the chiasm was concerned. In this group there were no adhesions around the chiasm, and the secondary optic atrophy was evidently due to internal hydrocephalus. For that reason exploration of the chiasm is not warranted. Whether any other surgical procedure might aid in restoration of vision to these patients is difficult to say.

Dr. Kaplan's reference to the diagnosis in case 1 is important, for the syndrome in this case might well have been due to a suprasellar neoplasm. In fact, the

cases of chronic nonsyphilitic chiasmal arachnoiditis were discovered through error of this type. Surgeons have frequently explored the base of the brain for neoplasm in the region of the sella turcica, only to find adhesions around the optic chiasm instead.

PHILADELPHIA NEUROLOGICAL SOCIETY

TEMPLE FAY, M.D., *President, in the Chair*

Regular Meeting, Nov. 24, 1939

Eminent Opium Users. DR. N. S. YAWGER.

Baudelaire, the French poet, used alcohol, opium and hashish. Robert Louis Stevenson; Madame de Stael; William Wilberforce, English philanthropist; Dr. Samuel Johnson, and Lord Erskine all used opium, as did Thomas Wainewright, English essayist, forger and poisoner. Jean Coteau is the author of "Opium: The Diary of an Addict"; Swinburne was notoriously alcoholic; Rossetti, painter and poet, used chloral, and Elizabeth Siddal, first his model, then his mistress and finally his wife, used laudanum. Of the innumerable persons who have taken drugs, some have done so from time to time; others continuously, or almost so.

Avicenna.—This famous Arabian physician and philosopher was born in 908 A. D. He prescribed opium extensively and finally became an addict. Of his old age, Lombroso said: "He plunged into debauchery and took opium to excess so that it was said of him that philosophy had not enabled him to live honestly, nor medicine to live healthily."

Paracelsus.—Two words coined by this genius still live—one the name by which he is best known, suggesting that he considered himself greater than Celsus, and the other laudanum, which he used so successfully in his practice and which it is believed he used personally. A strange but not improbable story for those times was that in infancy he had been castrated by some drunken soldiers who had taken temporary possession of his father's house. Whether through violence or natural causes, Paracelsus was regarded as not being sexually normal; he had little or no beard, never married, hated women and was not known to have had sexual relations with them. Though self taught, early in his professional career he became professor of medical science at Basel, but he soon brought such resentment on himself that he was obliged to leave. His practice was very large, but it is believed he caused many persons to become opium addicts.

Thomas De Quincey.—The fragment of autobiography entitled "Confessions of an English Opium Eater" has been widely read, partly through curiosity aroused by its unique title and partly for its believed literary merit. De Quincey came of a psychopathic family. Probably with an inherent hedonic tendency, he began to use opium while he was a student at Oxford, with "gastric distress" as the assigned reason. He stated that at times he used from 10,000 or 12,000 drops of laudanum daily. Strangely, though opium leads to impotence, his wife bore him eight children. However, only one had more than average intelligence. Some critics spoke of him as rough, rude and sinister, with logic that was more apparent than real.

Samuel T. Coleridge.—Of him Carpenter said: "There was probably no man of his time, or perhaps of any time, who surpassed Coleridge in the combination of the reasoning powers of the philosopher with the imagination of the poet and the inspiration of the seer . . . and yet there was probably never a man endowed with such remarkable gifts, who accomplished so little worthy of them." In 1807, he became a wanderer, leaving his brother-in-law, Southey, to care for his family. The first estrangement from his wife came when he was indulging unduly in

opium, and subsequently they separated permanently. There were four children, the youngest being a daughter, both charming and brilliant. She showed some of her father's intellectuality, without his weakness of character. Coleridge conceived the idea of founding a democratic colony on the Susquehanna River. The principles were to constitute "pantisocracy," embodying equal government by all and entire generalization of individual property. Lectures were given and considerable money was subscribed, but Southey had to carry on most of the propaganda and so the project was finally abandoned. At times the quantity of laudanum Coleridge consumed was enormous. It was said that "his customary consumption was from two quarts a week to a pint a day." He once told a friend he was "fast sinking into an opium sot." Eventually, there being no hope of his abandoning its use on his own accord, he became a permanent member of a physician's family, where the quantity consumed was greatly reduced. He also used snuff and alcoholic beverages, and he once wrote: "We will have a fair trial of bang [hashish]."

Edgar Allen Poe.—Born of actor parents, Edgar's father disappeared during his infancy and his mother died shortly after, of tuberculosis. There were three children: William Henry died at 24, of tuberculosis and alcoholic excesses; a sister, Rosalie, was a moron. Soon Poe became a foster child in the home of the rich, but stern, John Allen. While at the University of Virginia he drank and gambled. On learning of his character deviations, Allen refused further advance of money, and Poe was obliged to leave the university. For a time he was a soldier in the United States Army under an assumed name, and, misrepresenting his age as not more than 21, he succeeded in entering the West Point Military Academy, but was later dismissed, after a court-martial. Two factors other than alcohol influenced this psychopathic personality—a strange compelling sexual nature and the use of opium. Poe finally found a home with Mrs. Maria Clemm, an aunt on his father's side. Soon Mrs. Clemm planned and consummated a marriage between her daughter Virginia, aged 13, and Poe, aged 25. Baudelaire, himself a user of opium, saw its effects in various of Poe's writings, especially in "The Tales of the Folio Club." An acquaintance said he "never knew the time when Edgar was not in love." Psychologically, according to Krutch, "there is good reason to believe this amorous young man avoided all sexual relations with any woman . . . his entire life from childhood until death was an almost unbroken series of hectic flirtations; and yet at the very beginning of his career, he deliberately tied himself to a child with whom, at least, after marriage was arranged, sexual relations would be impossible." Poe's wife died at the age of 24, and he lingered but a short time after. Never with sufficient self control, he continued to drink and had delusions of persecution. His self pity was enormous, and his exploitation of the emotion of fear showed a definite sadistic trend.

John Randolph.—This American statesman, who claimed descent from Pocahontas, was by education a lawyer and by choice a politician. He became a member of Congress and leader of the administration party, later a senator and finally minister to Russia. His eloquence, sarcasm and wit, together with his various eccentricities, made him for years the most talked-of American citizen. Randolph was a proud member of a very proud Virginia family. Shortly after his nineteenth year, it became known that he was impotent. He was tall, lean and always boyish in appearance; he was almost beardless and had a high-pitched voice, traits that suggest the eunochoid state. Being exceedingly proud, and the only one of three boys to live beyond early adult life, impotence was doubtless a cause of his embitterment. One biographer, with less restraint than others, has told of the great family scandal. Richard, the oldest brother, had always been John's intimate and beloved companion. When suddenly meeting a friend one day, John was made aware of the scandal that had become common knowledge. Within Richard's family was Nancy, an alluring sister-in-law. It was charged that he was the father of a child born to Nancy and that in an effort to conceal the offense the child had been put to death. Richard was brought to trial, and two of the defense

lawyers were Patrick Henry and John Marshall. By reason of the prosecution failing to make out its case, the trial ended abruptly. Richard died shortly after. John had always hated Nancy, and he was further incensed when she later told him she had given birth to a child but that it was born dead; furthermore, that it was the youngest brother, Theo, who had died a few weeks later, who had seduced her; Richard, who had known all the facts, had endeavored to protect her by concealing them. Subsequently, Nancy married the elderly Gouverneur Morris, of New York. Later, unfortunate rumors concerning Nancy again reaching Randolph, he informed Morris of Nancy's previous disgrace. Randolph was given to alcoholic excesses; with regard to opium, one writer said it was "generally understood that his addiction to the habit was of many years' continuance and lasted until death." To a friend Randolph once said: "I live by if not on opium."

Conclusions.—Paracelsus' excessive use of opium in practice and the publication of De Quincey's "Confessions" were followed by great misuse of opium. As a result of international, national and state control, abuse of narcotics is decreasing. It is thought that more than 10 grains (0.65 Gm.), or at most 20 grains (1.29 Gm.), of morphine is not effective, greater amounts being without action because of the characteristic tolerance. No convincing theory has been advanced to account for this tolerance. It has been suggested that the body may acquire power of rapid elimination or ability to destroy the narcotic, that antibodies may be developed or that the nervous system may become "dulled" to the effects of the drug. That De Quincey could consume such large quantities of opium and remain potent sexually may seem incredible. Perhaps there was some exaggeration. Besides, it appears that the amount of the narcotic used was greatly reduced at times, when impotence may have ceased temporarily. Furthermore, all addicts do not become impotent. Three of the opium users discussed here, Paracelsus, Randolph and Poe, were more or less sadistic and were believed to be impotent. This is but surmise: An outstanding world leader who is unmarried but who delights in having attractive women about him is believed to be sexually unresponsive. Perhaps he, too, is impotent, with resulting embitterment that may find expression in sadistic acts.

Clinicopathologic Consideration of Displacement and Herniation of the Hippocampal Gyrus Through the Incisura Tentorii. Dr. Gabriel A. Schwarz, New York (by invitation), and Dr. Albert A. Rosner, New York (by invitation).

As one of the causes of secondary, distant or false localizing effects of space-taking intracranial lesions, recent attention has been focused rightfully on the "temporal pressure cone." This refers essentially to the medial displacement and herniation of the hippocampal gyrus and immediately adjacent structures into the potential space that lies directly above and between the free edges of the tentorium cerebelli and the brain stem as the latter structure passes through the incisura tentorii. We have studied the pathologic and clinical characteristics of this type of herniation. Our material for the pathologic investigation consisted of 100 brains with different types of supratentorial space-consuming lesions. The clinicopathologic relationships were studied in 43 cases especially selected because of the marked hippocampal herniations observed at autopsy. These cases were contrasted clinically with 21 cases of supratentorial space-taking lesions carefully selected so as to exclude any local pathologic condition.

Pathologic Observations.—Indentations of a linear configuration on the orbital surfaces of the hippocampal gyri had been noted for many years in the department of neuropathology of the Neurological Institute of New York. As was subsequently proved to be correct, these indentations were thought to be the result of pressure of the free edges of the tentorium cerebelli on the displaced hippocampal tissues and were called "tentorial grooves." Measurements were made in each

case from the most mesial tip of the uncus laterally to the indentation (groove distance). The depth, length and extent of the tentorial grooves were described qualitatively. Tentorial grooves, short, shallow, and equal on the two sides, were noted occasionally in normal brains at autopsy. With increased intracranial pressure from other causes, we have also noted shallow, short and bilaterally equal grooves with slight groove distances. Tentorial grooves were noted in 83 per cent of our cases. Nine brains showed marked and bilaterally equal grooves; these were associated chiefly with frontal parasagittal lesions. Seventy-four brains showed unequal hippocampal displacements on the two sides. Twenty-five of these presented groove distances on one side of 10 mm. or more. In 56 of these brains (in which the laterality of the cerebral lesion was evident) the hippocampal herniation was observed to be ipsilateral to the tumor. Unilateral cerebral lesions, in the temporoparietal region notably and in the temporal lobe particularly, produced most marked unilateral hippocampal herniations. Associated with hippocampal herniations was contralateral shift of the brain stem, hypothalamus and optic chiasm and tracts, with distortion, rotation and compression of these structures and, less frequently, hemorrhages in the brain stem and the hippocampal, fusiform and occipital gyri. The most significant causal factor in this pathologic complex was apparently the location of the space-taking lesion. The size of the lesion, in the sense of its space-occupying qualities, was probably of almost equal importance. The histologic character and the rate of growth of the cerebral mass were of questionable significance. Bilateral hippocampal herniations tended to squeeze the brain stem and produce flattening of the mesencephalon, with narrowing of the sylvian aqueduct. In only 22 cases was there an associated cerebellar pressure cone. In 35 cases dilatation of the lateral and third ventricles was thought to exist.

Clinical Findings.—It appears that there is a group of signs and symptoms which occurs frequently in cases of marked hippocampal herniation. In the order of frequency, the manifestations before operation (in the sense of any procedure altering equilibrium of the intracranial pressure) are: (1) fluctuations in the state of consciousness, (2) anisocoria with or without dysfunction of the pupillary light reflex, (3) nuchal rigidity, (4) imbalances of extraocular muscles, (5) cardiorespiratory and thermoregulatory disturbances, (6) paradoxic and shifting signs of involvement of the pyramidal tracts, and (7) decerebrate rigidity. Similarly, postoperative symptoms are: (1) marked respiratory difficulties, with failure of respiration before cessation of heart action, (2) thermoregulatory upheaval, resembling the neurogenic fever of Erickson, and (3) cardiovascular disturbances. These signs and symptoms occurred irregularly. All were invariably exaggerated by lumbar puncture, encephalographic and ventriculographic procedures or craniotomy. Supportive measures, as used routinely to correct the disturbances mentioned, invariably failed.

What is the necessity for diagnosis of herniation of the hippocampal gyrus? We believe that the occurrence of this complication with a supratentorial space-taking lesion alters the prognosis. Such a herniation presents a grave hazard to the clinician, with lumbar puncture and taking of encephalograms, and to the neurosurgeon, with ventriculographic and decompressive procedures and osteoplastic craniotomies. It may mean sudden death, disturbed states of consciousness, loss of favorable operative factors or complicating, misleading signs and symptoms. The surgeon must recall that removal of part, or even all, of a supratentorial space-occupying lesion may be a futile procedure, for the complicating hippocampal herniation may not be released and, with the brain swinging back into the place of the lesion, further distortion and compression of the brain stem and hypothalamic region may occur, with irreversible changes in these vital structures. Subtemporal decompression, although much less used today, is certainly contraindicated with such a herniation. If the lesion happens to be on the left side of the brain, the decompression is usually placed on the opposite side to avoid damage

to the left temporal lobe. This only adds insult to injury, for such release of pressure on the side opposite a herniation is conducive to furthering that herniation. Even if the decompression is ipsilateral, the shift of cerebral structures may be dangerous when the hippocampal herniation is not spontaneously reducible. Hence it seems that in the presence of a temporal pressure cone certain procedures intended to relieve the increased intracranial pressure may be contraindicated, and may be considered only after proper treatment of the herniation. The clinician in dealing with supratentorial intracranial tumors should be wary of certain signs and symptoms, in order not to be misled in localizing the primary lesion. It should not be difficult to suspect the occurrence of a hippocampal herniation if the observer always has its possibility in mind.

DISCUSSION

DR. B. J. ALPERS: I have had the pleasure of reading this paper, so I have an advantage over most of the members, for it is a long, well written and scholarly review. It marshals many observations on herniations of the brain, which fit well together. There has always been a question in my mind whether herniations such as one sees at autopsy have any real significance. I have never paid much attention to them until recently. From the prognostic viewpoint, herniation might be regarded as a decompression effect rather than as evidence of pressure. I have found it difficult to understand how compressible tissue like the hippocampal gyrus, which is still soft at autopsy, can produce enough pressure to cause definite neurologic signs, especially when one realizes that the fifth and seventh nerves are frequently caught in tumors of the cerebellopontile region without evidence of their involvement. It is more probable that the signs are produced not by pressure but by pushing of the brain stem with pressure against the opposite incisura.

In spite of the careful analysis of Dr. Schwarz and Dr. Rosner, I am still at sea as to whether these symptoms can be caused by hippocampal herniation. These cases have served to call attention to the distant effects of tumor of the brain.

DR. S. B. HADDEN: The authors are to be congratulated on their presentation of an analysis of symptoms in this important syndrome. By this analysis one may eventually be able to make a clinical diagnosis of incisural hernia and devise a satisfactory method of management. I have had opportunity to observe several patients with incisural herniation, and in only 1 instance did I make an antemortem diagnosis. This patient presented symptoms of a typical tumor of the posterior portion of the frontal lobe. Suddenly there developed homonymous hemianopia, pointing to a lesion in the opposite temporal or occipital lobe. My explanation was that the incisural herniation had produced an occlusion of the posterior cerebral artery. This false localizing sign is the only definite indication of incisural hernia that I recognize. Most of the other symptoms that occur in conjunction with this lesion are similar to those associated with a pressure cone in the medulla. I note that in several of the authors' cases there was occlusion of the posterior cerebral artery. I have never seen this in cases of medullary pressure cone in which there was not incisural herniation.

The authors again call attention to the fact that increased intracranial pressure may cause symptoms of involvement of the cranial nerves although the cranial nerves involved are remote from the actual lesion. I believe it is time one realized that the cranial nerves, like any other nerves, may have their function destroyed by interference with their blood supply, as well as by destruction of their continuity through trauma. One seldom finds the sixth cranial nerve, which is involved in many cases of intracranial pressure, flattened or macerated by pressure. The disturbance in its function is probably due to interference with its blood supply. Increase in intracranial pressure produces many remote symptoms through interference with the blood supply. I hope that the mechanics of this process will eventually be more clearly understood. I believe not only that disturbances of the

cranial nerves secondary to increased intracranial pressure should be regarded as due to impairment in circulation, but that almost all the other symptoms of intracranial pressure should be considered as due to histanoxia.

DR. TEMPLE FAY: This presentation is extremely important and illustrates some of the conditions that constitute the risks in neurosurgical procedures. It is obvious that each one of this series of 100 specimens represents the patient's failure to survive the surgical or the diagnostic procedure. Without efforts at neurosurgical treatment, death follows inevitably, and the value of these procedures can be estimated only in terms of those who have survived. Each survival in reality is a triumph of surgical and diagnostic skill.

The existence of herniation of the incisura has been recognized for many years. I have devised an operative attack in cases of this lesion, the first objective being section of the incisura of the tentorium in order to relieve the herniation which may occur from above, as in these instances, or may be present from below if a large cerebellar lesion is causing expansion of the structures beneath the tentorium.

Careful recognition of this condition and proper management of pressure relations within the skull by means of "dehydration" or ventricular or spinal drainage have, I believe, been responsible for my so-called good luck in handling this problem. Under proper conditions I have not hesitated to make an encephalogram, provided adjustment of pressure and edema was assured. In other instances I have sectioned the tentorium before attacking the tumor.

The type of hemorrhage shown by Dr. Schwarz is, of course, recent from the standpoint of the patient's history and preterminal condition. This type of catastrophe and "respiratory death" indicates some crisis in which pressure or circulatory relations were acutely altered to produce the hemorrhage. I have seen such hemorrhages follow vomiting and straining. I have therefore hastened to cut the incisura as well as the tentorium as far as the lateral sinus, thus producing decompression of the posterior into the middle fossa or vice versa, and have removed the foramen magnum and ring of the atlas at the same time to prevent herniation into the foramen. Subsequent operative attack on the tumor may be required, as this procedure in itself is a major operation. The postoperative relief of pressure and a satisfactory convalescence have convinced me of the importance and value of the preliminary maneuver.

I recall many instances of "respiratory death" years ago, but I cannot recall within the past eight years such terminal respiratory-thermal crises, since I have carefully concerned myself with preventing cerebral edema and herniation through control of intracranial pressure by means of "dehydration." It is true that patients with terminal crises are sent to the neurosurgeon, and such patients survive only a few hours. In such cases the herniation has been allowed to occur as a result of uncontrolled pressure produced by ill advised spinal puncture.

With respect to Dr. Alpers' point, it is true that the symptoms can hardly be ascribed to the soft tissue comprising the peduncle, but closure of the incisura by herniation produces a block in the circulation of the cerebrospinal fluid, so that the cisterna pontis no longer has continuity with the upper pathways of absorption. This produces back pressure, in and around the fourth ventricle, with secondary anemia and symptoms of respiratory distress; section of the incisura and tentorium removes blockage of the fluid, and hence relieves the symptoms.

DR. ALBERT A. ROSNER: Dr. Alpers' point as to whether these herniations are a manifestation of spontaneous decompression is well taken. Increased intraventricular pressure is at least one of the factors that we think are responsible for the condition, the relation between the pressure within and that outside the ventricles playing an imporant role.

The question of involvement of the third nerve needs further elucidation. On the basis of our findings, the peripheral nerve is less likely to be involved than the brain stem itself. Moreover, it is probable that whatever effects are exerted in

the brain stem and related areas are due to secondary vascular rather than to primary pressure factors. The high incidence of hemorrhage in the brain stem in our series supports this thesis. Whether the herniation itself is directly responsible for the symptoms described must be decided by analysis of the cliniopathologic data. That intracranial pressure alone is not responsible seems proved not only by our own figures but by the work of Browder and his associates, who were able artificially to raise intracranial pressure to enormous heights without giving rise to the train of events we have described. Moreover, our experience tends to confirm rather than to deny the existence of distant effects of vascular pressure or occlusion.

Shifting of the whole brain mass, hardly unexpected, was indicated in 17 cases; in these cases the presence of herniation of the gyrus cingulus through the falx cerebri was revealed. This phenomenon alone, however, cannot be considered as an explanation of the symptom complex; the pathologic analysis contradicts such an explanation.

Dr. Hadden's diagnosis of an incisural herniation on the basis of a single sign reveals a high index of suspicion with regard to false localizing signs. There are many symptoms that appear to be more dependable, however. There were only 3 cases of infarction of the occipital lobe in our series.

It appears that any disturbance in cerebrospinal fluid balance, whether through the intraventricular or the lumbar route, is dangerous. There is no question that lumbar puncture played a role in the production of symptoms—in 8 of our cases lumbar puncture was a suspected agent. In five of these 8 cases death from respiratory failure occurred within twenty-four hours after the procedure. Such patients are admitted to the Neurological Institute in great difficulties, and one witnesses a tragic death. There is a high incidence of pontomesencephalic hemorrhage among these patients, the complication appearing post mortem in 6 of the aforementioned cases. Embarrassment of higher centers in cases of incisural herniation seems indicated by such symptoms as hyperthermia, irregularities in respiration and cardiovascular effects. Distortion of the base of the third ventricle has been seen in some encephalograms, but the origin of this cannot definitely be said to be the herniation.

We have no figures correlating the degree of increased intraventricular pressure with the incidence of incisural herniations. The question of lumbar puncture has already been discussed.

The pathologic changes in the herniated area have been investigated. The tissues in this area were soft, friable, discolored and hemorrhagic. We did not observe anything not previously described.

As to the incidence of deaths from respiratory embarrassment, there were 15 in this series.

Most attempts to release a herniation of this sort by operative means have been reported to be unsuccessful. I am not aware of Dr. Fay's work in this respect. It is necessary that the diagnosis of the condition be made before surgical intervention; it seems entirely within our means to predict the course of this complication in most instances.

As to pontomesencephalic hemorrhages seen post mortem, it has been our experience also that these were more recent than old. This was especially true in cases of death following lumbar puncture.

With regard to dehydration, this procedure, as might be suspected, has its repercussions in the cerebrospinal fluid system. In 1 of our cases decerebrate attacks as well as other signs were induced by intravenous injections of a hypertonic solution of dextrose. This raises the question whether the physiologic effects of this procedure are much the same as those of lumbar puncture.

In conclusion, it is important that this group of symptoms be understood on the basis of the underlying pathologic condition, and that they be thought of as a cerebral accident that may dominate and terminate the clinical picture at any time during its course.

MICHIGAN SOCIETY OF NEUROLOGY AND PSYCHIATRY

R. GORDON BRAIN, M.D., *President, in the Chair*

Regular Meeting, Nov. 30, 1939

Migraine and Trigeminal Neuralgia Occurring in a Neuropathic Family.

DR. RUSSELL T. COSTELLO, Detroit.

A detailed report is given of the occurrence of migraine, trigeminal neuralgia, psychopathic personality and other neuropathic traits and tendencies as recorded in a complete family tree, extending back to the middle of the nineteenth century. The migraine was found to follow primarily one line of descent, and the trigeminal neuralgia another, with infrequent instances of association of the two conditions in the same person. The line of descent was most marked in the female.

DISCUSSION

DR. LINUS J. FOSTER, Detroit: This excellent case presentation leaves little for discussion. All are aware of the evidence in favor of the hereditary nature of migraine and also, in many cases, of tic douloureux.

A cursory examination of the literature failed to reveal any reports of cases in which there was evidence of the two conditions being hereditary in the same family. I was interested in an article by Wilfred Harris (*Ann. Surg.* **103**:161 [Feb.] 1936) which dealt with the association of tic douloureux and disseminated sclerosis.

The only question I wish to ask Dr. Costello is whether the cases he described as those of tic douloureux possibly were cases of migrainous neuralgia.

Epileptic Phenomena Associated with Tumors of the Temporal Lobe.

DR. HAWLEY SANFORD, Detroit.

In an attempt to evaluate existing statements as to the association of epileptic activity and tumors of the temporal lobe, 211 cases of such tumors seen at the Mayo Clinic prior to 1937 were studied clinically and pathologically. In this group some epileptic phenomena were present in 129, or 61.1 per cent, of the cases. In the remaining 38.9 per cent of cases there was no epileptic activity. In 96, or nearly half (45.4 per cent) of the cases, there were generalized or grand mal convulsions. In 24 additional cases, or 11.3 per cent, there were jacksonian seizures, the number of patients having some form of major epileptic attack being thus 120, or 57 per cent of the 211 cases. There were also records of 96 cases in which some sort of minor epileptic manifestation had been mentioned. These were distributed as follows:

	Number of Cases	Percentage of Total Group
Olfactory hallucinations	32	15.1
Petit mal seizures	29	13.7
"Epigastric fear" seizures	19	9.0
Gustatory hallucinations	17	8.5
Dé jà vu	11	5.2
Amnesic fugues	2	0.9
Micropsia	1	0.5

Two or more of the phenomena mentioned in the accompanying tabulation frequently appeared together, sometimes in a complex formulation originally referred to by Hughlings Jackson as the "dreamy state."

This statistical study serves as a reminder that the occurrence of convulsions or of any of the minor manifestations of epilepsy demands a thorough search for a possible tumor of the brain, especially if they make their appearance during the middle years of life. If evidence of a space-consuming intracranial lesion is discovered, the fact that the patient has demonstrated any sort of epileptic attack points to the temporal lobe as the possible site of the lesion. If certain

minor epileptic activities, especially olfactory hallucinations, have been present, the localization is more certain. This may prove of considerable value, since other localizing signs, even visual field defects, may be absent.

DISCUSSION

DR. FREDERIC SCHREIBER, Detroit: My first acquaintance with Dr. Cushing began in 1922, when, as a fourth year medical student, I asked him to give me an *Arbeit.* He wrote on this slip of paper, which I have kept: "Are uncinate seizures of lateralizing value?" On reviewing the 39 cases of verified tumors of the temporal lobe associated with uncinate seizures in the series of the Peter Bent Brigham Hospital at that time, I found that in all those in which pleasant or nauseatingly sweet odors were present the tumor was in the right temporal lobe. In three fourths of those in which foul or disagreeable odors were present the tumor was on the left side. The findings in such a small series of cases may not be significant, but the study marked the beginning of my interest in this subject and led to my later association with Dr. Cushing as a surgical pupil.

Dr. Sanford's detailed report gives an excellent picture of the symptoms to look for in cases of tumors in the temporal lobe. Why do such tumors reveal themselves by convulsions, uncinate fits, aphasia or hemianopia? Why do the symptoms disappear in many cases after surgical intervention? It is my belief that these neurologic manifestations are the result of localized cerebral anoxia secondary to interference with the circulation in the temporal lobe and adjacent areas.

Recently, I operated on a man with an astrocytoma of the left frontotemporal region whose first jacksonian convulsion of the face began as he descended from the cogwheel car on Pike's Peak, where the oxygen supply is about one-fourth less than that in the air the patient was accustomed to breathe in Detroit. This is a human example of what Gellhorn has been demonstrating in animals. Additional lack of oxygen in an animal the cerebral cells of which are already restricted in utilization of oxygen produces convulsions, even though no clinical symptoms are evident when only one of the two conditions for anoxia is present.

The natural response of any nerve cell to anoxia is unbridled exhibition of its normal function. Peripheral thrombosis elicits intractable pain in an extremity; an anoxic motor cell group reacts with a convulsion in the muscles normally supplied with motor function; the cells of the island of Reil reveal their oxygen embarrassment with abnormal olfactory responses. Possibly the actual mechanism by which the dying cerebral cell manifests its distress is an abnormal electrical discharge. If the cells involved are dead, the surgeon cannot expect recovery of function after relieving the local pressure on the vascular and cell structures. The response to surgical intervention, however, in many cases of tumor of the temporal lobe is the ordinary response to abolition of anoxemia, with recovery of cell function. It may be that if there is doubt as to the diagnosis of a tumor of the temporal lobe, one might subject the patient to an atmosphere deficient in oxygen in order to bring out any latent localizing symptoms.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

GILBERT HORRAX, M.D., *President, in the Chair*

Regular Meeting, Dec. 14, 1939

Treatment of Delirium Tremens. DR. CHARLES M. KRINSKY, New London, Conn.

The lack of uniformity of opinion among those who have to treat patients with delirium tremens prompted a study of such persons admitted to the Boston Psycho-

pathic Hospital. Mortality statistics have varied as a result of limited resources, the variety of clinical material or difference in diagnostic criteria. Nevertheless, it has been possible to lower the mortality rate from 37 per cent, in 1911, to approximately 4 per cent, in 1936. It is my purpose in this paper, first, to discuss the treatment of delirium tremens at the Boston Psychopathic Hospital, where the mortality rate over a twenty-five year period has been 3 per cent, second, to analyze and evaluate other therapeutic regimens and, third, to report a rise in the incidence of psychoses due to alcohol since the repeal of the prohibition amendment.

Between 1913 and 1938, 860 patients with delirium tremens were admitted to the Boston Psychopathic Hospital. Of this number, 82, or 9.5 per cent, were women. There were 25 deaths in this series. The total number of patients admitted to the hospital for this twenty-five year period was 49,531, 3,522, or 7.1 per cent, of whom were persons with alcoholic psychoses. Patients with delirium tremens constituted 24.4 per cent of those with psychoses due to alcoholism.

With minor modifications, the treatment for delirium tremens at this hospital has been notable for its simplicity. The general principles have been good nursing care, absence of restraint, withdrawal of alcohol and attention to food and fluid intake and to sleep. Vitamins need be given only when evidence of peripheral neuritis is present. Paraldehyde seemed to be without a peer for producing sleep. Hydrotherapy was not prescribed in cases of severe type, for death may follow such treatment, probably as a result of disturbance of the mechanism for temperature control. Enemas were of great benefit in any case of delirium tremens. Fluids were not restricted, and lumbar puncture and morphine were not employed. Work by Thomas and his collaborators showed that elevation of pressure of the cerebrospinal fluid did not occur in cases of delirium tremens and that dehydration measures were not indicated.

It seemed fairly conclusive that the low mortality rates obtained by the advocates of either the dehydration or the hydrotherapy group resulted from better individual care of the patients.

It is significant from the point of view of prevention that in the five year period (1934 to 1938) after the repeal of the Eighteenth Amendment, the increase in the number of patients with delirium tremens admitted to the hospital was 41.6 per cent and that of all patients with psychoses due to alcoholism was 35.7 per cent, while the increase in the total number of patients admitted was only 7.5 per cent, as compared with the corresponding figures for the five year period (1928 to 1932) before repeal. This elevation of the level of incidence of the psychoses due to alcoholism since the repeal of the Eighteenth Amendment should be considered of social, as well as of psychiatric, importance.

Psychologic and Clinical Aspects of Space. DR. ERWIN STRAUS, Black Mountain, N. C.

Space is at once a very old and a very new subject of science. Although philosophers and scientists ever since the Greeks have discussed the complex problems of space, new views have been expressed during the last decades. This could happen only because space is familiar, but nevertheless completely unknown. In everyday life one is not much concerned with the problems of space; it is taken for granted that space exists, that there are many things within space and that one can move through space. Scientific inquiry has not fundamentally changed this attitude. It attempted only to understand more thoroughly the structure of space. The subject remained *the* "objective" space; its relation to matter, to things, to motion, to mind, to God, its finite or its infinite character, and so forth. It was only by metaphysical and epistemological doubts of the reality of perceptual things that psychologic questioning was brought into discussion.

From the beginning, a somewhat negative tendency was manifested with these considerations. The illusory appearance of sense impressions must be reduced to that reality which lies at the base of them. This tendency has continued in many

forms up to the present; the question how far—at least for psychology—this reduction is meaningful has for the most part been neglected.

Since the sixteenth and seventeenth centuries, knowledge of space has increased its importance for the understanding of everything in nature, the psychic life not excluded. From this time, space has been the euclidean space of three dimensions. Metaphysical and epistemological reasons again led to the erroneous interpretation that even psychic life could exclusively and completely be understood as processes in *the* space and *the* homogeneous time. The theoretic principles of physiologic psychology, developed only during the nineteenth century as an independent branch of science, were established long ago by Descartes and Hobbes. The attempt to explain psychic life by methods quite strange to it confused the problems and obscured the phenomena to the view of the investigators.

It is not more than a hundred years since mathematics and, later, physics became unwilling to accept as axiomatic the euclidean structure of space. Psychology cannot take over the specific use of time and space formerly developed by physics, but is indebted to it for new liberty in dealing with problems of space and time; psychology can now free itself from the compulsion to relate psychic life in structure and content to *the* space.

One can try again to investigate the phenomena in their full extent, regardless of rules which transferred from physics or physiology into psychology become mere prejudices. The way in which physiology may deal with the phenomenological discoveries is its own business. In any case, if the physiologist hopes that he can explain psychic experience he must first become aware of what he wants to explain.

As an introduction to the phenomenology of space one may use an analysis of dancing. Dancing is for its universality and autochthonous origin a legitimate, but nevertheless somewhat neglected, subject of psychology. Experience seems to show an invariable relation between dancing and music, or at least between dancing and rhythmic sounds. Is this relation an accidental or an essential one? Can one understand dancing as a process within the organism or as an attitude toward the world? One understands dancing only as an intrinsic relation between a particular kind of experience, a particular kind of motivity, a particular form of space and a special sensual area. Accordingly, there is a psychology of motion with problems of its own which should not be confused with those of the physiology of motion. A comparison of motions of dancing and of purposive action, of their respective forms of space, of their kinds of experience, of their true sensual areas may help one to understand better the nature of both.

The general results of this analysis may be summarized as follows: 1. Sense perceiving (*das Empfinden*) cannot be understood as the mere presence of sense data; it is a double-faced relation of an ego to its world. 2. Every sense reveals the world in its own peculiar way. 3. By the different sense perceivings (seeing, hearing and the like) one is for a time being in different communications with the world. 4. The intrinsic connection of perceiving and self motion cannot sufficiently be explained as a connection of sensorium and motorium. 5. Different forms of space and of self motion correspond with the different kinds of perceiving. 6. Perceiving is a kind of psychic experience preceding and quite different from knowing; it is common to man and animals. 7. The forms of space belonging to perceiving and self motion have distinctive, primary physiognomic qualities. 8. Out of the physiognomic space, by means of progressive abstraction, the higher forms of the geographic, geometric, physical, historical and esthetic space are evolved. 9. In everyday life, physiognomic and geographic space interpenetrate. From landscape one constructs geographic space, but one must relate the horizonless geographic space, with its places determined in a general way, to the perspective of "here" and "there" if one wishes to act and to move oneself. 10. One does not perceive space as an object opposite one but experiences oneself within space; space is developed for one in accordance with one's potentiality of motion. 11. Because sense data have their specific temporal-spatial structure and physiog-

nomy, they make possible and define in detail such human creations as language, music, dancing and architecture. 12. While dancing, one realizes the particular ecstatic kind of experience, turned away from action, duty and historical existence. 13. The subject of perceiving can be understood only as a being in a state of becoming and essentially mobile.

These views may help one to understand better many clinical symptoms and syndromes, e. g., some agnostic and apractical disturbances, depersonalization, addictions, hallucinations and schizophrenic symptomatology. The relation of phobias to the primary physiognomic qualities of space is striking.

NEW YORK NEUROLOGICAL SOCIETY

E. D. FRIEDMAN, M.D., *President, in the Chair*

Regular Meeting, Dec. 5, 1939

Preganglionic Outflow to the Extremities. DR. DONAL SHEEHAN and DR. A. S. MARRAZZI (by invitation).

The wide adoption of sympathectomy for vascular lesions has necessitated more exact knowledge of the anatomic relations of the sympathetic pathways, in particular in the cervical and lumbar regions. This became increasingly evident when cervicodorsal sympathectomy proved inadequate for the relief of vasospasm in the upper extremity, whereas lumbar sympathectomy permanently cured the condition in the leg. More recently, White and Smithwick and their co-workers have offered as an explanation for these variable results the fact that smooth muscle when deprived of its nerve supply becomes hypersensitive to epinephrine; they made the further observation that preganglionic section of the vasomotor nerves renders the blood vessels less sensitive to circulating epinephrine than does complete denervation by postganglionic excision. The physiologic observations of White and Smithwick have been confirmed in animals by Ascroft and by Grant, and in man by Simmons and Sheehan. That they do not offer an entire explanation of "relapse" following sympathectomy has been demonstrated by Simmons and Sheehan, but the importance of the preganglionic operation, leaving the postganglionic cell stations intact, has been firmly established.

Present knowledge of the course of the preganglionic nerve fibers in man is based largely on the early experiments of Langley and Bradford and Bayliss, carried out on dogs and cats and using erection of hairs and sweating as criteria of sympathetic activity. More refined methods of recording nerve impulses are now available. During the past year we have utilized the oscillographic method of recording nerve impulses in attacking this problem. After stimulation of certain ventral spinal nerve roots, we have been able to pick up from the sciatic and femoral nerves action potentials which have proved to be sympathetic according to the following criteria: (*a*) The sympathetic chain is the only anatomic connection between the root stimulated and the nerve from which the action potentials were recorded; (*b*) the action potentials were in the C-B wave band; i. e., they represented slow-conducting fibers; (*c*) the action potentials were abolished by intravenous administration of nicotine.

Each ventral root from the seventh thoracic to the sixth lumbar, and thereby the preganglionic fibers emerging at these levels, was severed from the cord, insulated from surrounding tissues and stimulated by accurately controlled shocks from a thyratron stimulator. The activity resulting in the sympathetic fibers in the sciatic and femoral nerves was detected by electrodes placed on the main branches of the ipsilateral nerves and connected with a direct current amplifier actuating a Matthews oscillograph. The B and C waves thus recorded enabled us to map readily the exact roots of origin of the myelinated and the unmyelinated

sympathetic fibers to the limbs. By recording from the contralateral nerves while repeating the stimulus to the original ventral root, we obtained data on the extent of crossed pathways for these fibers. Since all slowly conducting fibers (i. e., B and C fibers) are not exclusively autonomic, the possibility that some of the B and C waves picked up might have originated in antidromically stimulated afferent fibers was considered and excluded by the fact that the intravenous injection of nicotine, which acts on sympathetic ganglia, was effective in blocking the previously recorded impulses.

DISCUSSION

DR. H. G. WOLFF: These investigators have raised the problem of increased sensitivity after denervation. One sometimes forgets that such increased sensitivity is not peculiar to smooth muscle. Indeed, in the higher mammals denervation of skeletal muscle also increases the response of that muscle to acetylcholine.

In the case of smooth muscle, postganglionic sympathectomy greatly increases the sensitivity, but preganglionic sympathectomy also increases it. Hempel indicated that the sensitivity after postganglionic sympathectomy was perhaps twice that after preganglionic sympathectomy. What is the cause of this phenomenon? Cattell and I, some time ago, approached this problem and offered an explanation. We used the nictitating membrane of the cat as a test object. We first severed the cervical portion of the sympathetic trunk between the inferior and the superior ganglion, and in that way produced a postganglionic preparation. After this we found that the sensitivity of the nictitating membrane to injection of epinephrine was increased. If, however, an electrode was placed on the superior sympathetic ganglion in such a way as to stimulate it for sixty or ninety seconds, it was possible to show with injection of epinephrine into the blood stream that this sensitivity had disappeared. It was absent for twenty minutes, after which it gradually returned. In other words, if we were able to produce a sustained contraction in this muscle for a minute and a half the sensitivity of the nictitating membrane to epinephrine more nearly approached that on the opposite, or normal, side. We inferred from this that the prolonged inactivity due to disconnection from the central nervous system had increased the sensitivity of the smooth muscle of the nictitating membrane to the circulating epinephrine.

In man it is possible, in the case of the upper extremity, to perform preganglionic section and to prevent rapid regeneration, which has been the difficulty with that procedure, by properly burying the cut end. If this is not done, regeneration, at least as indicated in the cat, may be well under way within a month. Our experience with patients shows that no such rapid regeneration occurs if the stump is properly buried. The question, then, is not whether there is no increase in sensitivity with preganglionic as compared with postganglionic sympathectomy, but how much there is.

The method that has been introduced tonight represents an advance. In concept the approach is simple. In practice, however, it is exceedingly difficult. To be able to interpret the A, B and C waves requires skill. I wish to ask—perhaps the authors have already done so—whether Langley's old assumption that nicotine acts only or primarily at the synapse may be assumed in such subtle experiments as these. Is it possible that the small motor fibers to skeletal muscle conveying slow-moving nerve impulses are affected by nicotine and that these changes could be brought out by the oscillograph? This is doubtful, but the effect of nicotine on such fibers should be ascertained.

The method described this evening is the only one so far available that will allow one to correlate the functional and anatomic components of a mixed nerve. Aside from being even more delicate, perhaps, than the movement of a hair, a change in the blood supply of a part or the absence or presence of sweat, it is the only way one can approach the question of what autonomic fibers are in a mixed nerve.

DR. MORRIS B. BENDER: I did not hear the entire paper, so that I do not think I am able to discuss it adequately. In line with what Dr. Wolff said about

the denervation of smooth muscle, it is known that denervated skeletal muscles are very sensitive to acetylcholine. This suggests the possibility that the motor nerves which supply these muscles contain autonomic fibers. The function of these fibers is more parasympathetic than sympathetic. In other words, it is possible that in all perfusion experiments in which acetylcholine is obtained by stimulating the motor nerve, the results are due to activation of the autonomic rather than of the motor nerve fibers.

DR. DONAL SHEEHAN: I wonder whether our observation that the hypersensitivity to epinephrine diminishes with time may not fit in with what Dr. Wolff has said of the disappearance of hypersensitivity of muscle after prolonged activity, for some time after preganglionic section or ganglionectomy the smooth muscle of the blood vessels does regain its inherent muscular tone to a certain degree. That is true not only of blood vessels but also of the smooth muscle in the intestine, in which after any type of peripheral nerve section the tone ultimately returns to a certain extent. Cutting of sympathectic fibers to the limbs may abolish the tonic contraction of the smooth muscle completely, and then as it returns, even partially, the sensitivity may become less.

The question of the exact pharmacologic action of nicotine will have to be answered by Dr. Marrazzi.

I know of no other anatomic connection except the sympathetic chain by which impulses can be picked up from the sciatic nerve on stimulation of the first, second and third lumbar roots, for sciatic nerve in the cat, even in a prefixed plexus, never arises higher than the sixth lumbar root. I am sure, therefore, from the anatomic standpoint, of the autonomic origin of the potentials, and the results following nicotine support this view.

DR. H. G. WOLFF: Is that not what you are trying to determine by your new method, namely, whether mixed nerves do or do not contain autonomic fibers?

DR. DONAL SHEEHAN: Yes, but anatomic dissection of a pathway is a well recognized method of approach.

DR. H. G. WOLFF: Are you not, therefore, introducing a supposedly more refined method to demonstrate what is already known to be a fact?

DR. DONAL SHEEHAN: True, but the anatomic arrangement of the lumbar and sacral nerves is such that I feel more sure of the autonomic nature of any action potentials which I may pick up from the sciatic nerve on stimulating the first, second and third lumbar roots than I do on stimulating, for example, the sixth and seventh lumbar and the first sacral roots.

DR. A. S. MARRAZZI: It is hard to give an answer based on our own experience to the question concerning the site of action of nicotine because of difficulties that arise in performing the proper experiments. However, it is classic pharmacologic knowledge, beginning with the work of Langley *(Proc. Roy. Soc., London,* s.B **46**:423, 1890; *J. Physiol.* **27**:224, 1901; **33**:374, 1905) that the action of this substance when used in a minimal dose and injected intravenously is limited to the synapse. I am aware that Chauchard *(Compt. rend. Soc. de biol.* **124**:1290, 1937) has claimed, although it has not been confirmed, that there is a change in chronaxia in addition to the effect on the synapse, but this observation concerned the local application of nicotine and is therefore of minor significance. (Nicotine has a similar toxic action on nerve trunks. [Pi Suñer, A., and Raventos Pijoan, J.: *Compt. rend. Soc. de biol.* **114**:97, 1933. Barry D. T.: *ibid.* **120**:294, 1935. Schwartz, S. D.; Sturtevant, M. C., and Thienes, C. H.: *Proc. Soc. Exper. Biol. & Med.* **35**:632, 1937]). I realize that to resort to classic knowledge is not the most satisfactory answer to the question concerning C fibers in the dorsal roots, but I have another point directly related to this: When, in a few experiments, we stimulated the dorsal roots, we did not with the strength we used obtain a potential in the sciatic nerve. However, it is possible that, although we did not obtain it in these experiments, we might have obtained it in others, and it was for the purpose of avoiding this complication that we used nicotine.

Dermoid Tumor in the Foramen Magnum with Astereognosis and Dissociated Sensory Loss: Report of a Case. DR. EDWIN A. WEINSTEIN (by invitation) and DR. ISRAEL S. WECHSLER.

This paper will be published in a later issue of the ARCHIVES.

Peculiar Manifestations of Memory, with Special Reference to Lightning Calculators. DR. A. A. BRILL.

I first saw the patient, a lightning calculator, in 1917, when he was 6 years old. He had never been to school, could neither read nor write and did not know any figures. His talent to add many columns of figures of five and six digits with phenomenal speed and accuracy was discovered accidentally. He could not subtract or multiply. I examined the boy after his ability had been demonstrated before a few medical and lay organizations and he had been described in the newspapers as a child prodigy. I advised against exploiting the child through public exhibitions, and heard nothing more about him until 1938. I then learned that my advice had been followed, that the boy was sent to school at the age of 7 and that he was a good pupil. At the age of 9 or 10 he lost his talent and developed as an average person.

In comparing this case with many similar cases reported in the literature, I found that this sort of talent always began before school age and usually disappeared about the age of 9 or 10, and that it continued in those who were mentally defective or in persons, for example some shepherds, who had no opportunity to receive any education. This talent was also present in some persons who began life normally and acquired some education, but became defective later as a result of disease. There were also some persons who never lost this gift and became great mathematicians, but they all showed a direct mathematical inheritance, extending in some cases over centuries. The patient whose case is reported here had such an inheritance: His paternal grandfather was considered a mathematical wizard. The patient was the youngest of 13 children, 6 of whom were living. He was delicate throughout childhood and did not talk until the age of 4½ years. The gift was discovered a few months after the boy lost his mother and sister; at first the numbers had to be called out to him in terms of concrete objects, e. g., 3,487 peanuts. He not only gave the correct answer as soon as the last figure was called, but could repeat each figure in the order given for about an hour thereafter. I call this kind of memory mneme (Semon), which is defined as memory without consciousness, and believe it may be explained by Hering's vibration theory of memory.

DISCUSSION

DR. SMITH ELY JELLIFFE: I feel a definite ineptitude in discussing this paper. First, I was never a lightning calculator. Calculating was always difficult for me. Second, I know much more about amnesia than I do about mnesia. Dr. Brill has introduced an extremely interesting, and not unimportant, subject. I think one can say that there would never have been a lightning calculator without the relationships of numbers. Numbers are binding symbols whereby individuals may be brought together. Thus, the primitive Indian put up five fingers and then two fingers and pointed to the moon and made a little gesture, indicating to his companion that in five days, at a certain river crossing, at a certain illumination of the moon, they would meet and get the deer they were after. Numbers began to be used to make more precise such combined activities, to bring persons together for practical purposes. To me the paper presented is especially significant in that it deals with the relationship of numbers to the unconscious. In Dr. Semon's work on the mneme, to which Dr. Brill referred, he made some extremely interesting observations on the memory of plants. He noted that invariably some time between certain days in September and in October the leaves of the horse chestunt fall off. He then planted in various parts of the world horse-chestnut trees sufficiently developed to have leaves and demonstrated that practically all over the world, whether in the mountains or in the valleys, in Africa or in Alaska, the leaves

would fall at practically the same time; in other words, the falling of the leaves of the horse chestnut indicated a mnemic inheritance behind that type of phenomenon. What does all this have to do with numbers? It seems to me it has a great deal, because numbers enter into any such series of observations; that is, the interest of numbers. I suspect that had you and I lived in the day of Pythagoras we should all be automatic comptometers. We should all have a great many of the faculties to which Dr. Brill has called attention. We should know more about the significance of numbers, be more interested in them and be regulated by them.

I shall not discuss the study of numbers in the unconscious, but many interesting things appear if one is interested in gathering observations of that kind. I think it was before this society that I called attention to a little song or chant that used to be sung in Protestant churches. There is a Hebrew version, and there are also versions in many other languages. It is a song about numbers:

"Twelve are the Twelve Apostles.
Eleven of them have gone to heaven.
Ten are the Ten Commandments.
Nine is the moonshine, bright and clear.
Eight is the great archangel.
Seven are the seven stars in the sky.
Six are the cheerful waiters.
Five is the ferryman in the boat.
Four are the gospel preachers.
Three of them are strangers.
Two of them are lily-white babes, all clothed in green—oh!
One of them is God alone, and ever shall remain so."

What does it all mean? It is interesting, when one bears in mind the simple outline of such a story, what one can do with the understanding of number symbolism in the dream. It is a beautiful little key. Thus, "Three of them are strangers." What are strangers, after all? Remember that the origin of the word "husband" is from "stranger." Under a matrilineal society, the husband sneaked in at night and had to be out in the morning before the brothers and uncles had awakened. Husbands and strangers and a certain type of activity were thus all correlated. I am certain, nearly every time one of my patients tells me of a dream in which the number three appears, that I know just what he is up to in his fantasy, although he slips it behind such an innocuous little symbol. It is intercourse every time. The way in which the whole series of number symbolisms group themselves in one's unconscious activities is marvelous.

I have said nothing about these young lightning calculators, or about the libidinous investment of numbers and what that libidinous investment stands for, but there is no question, at least in my mind, and it is not a speculation, that behind the number symbolisms there exists a vast history of mnemic inheritance of community interest, which began with the binding of society.

DR. TRACY J. PUTNAM: Dr. Brill has presented an uncomfortable subject, uncomfortable because it is so difficult to correlate it with one's ordinary mechanical theories of brain function. It is taken for granted that a normal person has a certain memory and a certain ability in mathematics, and one is apt to explain this as an associational process; but how can this youngster, 6 years of age, have associations involving a column of seven numbers of seven digits, which cannot conceivably have come within his experience? It seems to me there are two aspects of Dr. Brill's presentation, a positive and a negative. The positive one involves the question of the mechanism of this extraordinary ability to deal with numbers. The negative one is the problem of why this child should develop and nourish the ability at this time of life, and later discard it. I have a great deal of sympathy with Dr. Brill's idea that the appearance and disappearance of the talent were emotionally determined. I know of a case of a similar talent in a child, of about the same age, which was apparently part of a severe compulsion neurosis; after long and determined treatment both the compulsion neurosis and the ability

to calculate disappeared simultaneously, and the child became more or less normal. It seems to me, however, that this does not go far toward an explanation of the positive manifestation. On the other hand, abnormal talents are not much more mysterious than normal ones. Every one can without counting estimate three, four or five objects at a glance. Gauss was able to estimate up to thirty or forty without counting them. It is conceivable that the first ordinary normal faculty is a matter of some fundamental human rhythm or arrangement of neural elements, and it is possible that the more complicated talent is also a utilization of more complicated neural elements. However, in the higher grades of these talents one enters into still more difficulty. It seems to me that this extraordinary ability with numbers transcends the faculty of memory. To be sure, an unusual memory is essential for adding large columns of numbers, but, to digress from this particular instance, there are the other geniuses who are able not only to add but to extract mentally the cube root of seven digit numbers. I know of an adult mathematical genius, an artist by profession, whose ability with numbers is not even a hobby. He keeps it rather hidden. He is able to perform extraordinarily complicated algebraic problems in his mind, involving large numbers, as long as he takes the problem as given and answers without pausing to think much; if he does he has the same difficulty which any one might have.

It is in relation to difficult subjects like this, for which one can give no satisfactory explanation, that it is of great importance to assemble the facts and survey them and reflect how little is known as an essential preliminary to better understanding of them.

DR. BERNARD SACHS: I hesitate to take part in this discussion, but there seems to be such a thoroughly happy family atmosphere here that I am willing to say a word. First, it has been a slight satisfaction to me to hear that there is something which the psychoanalysts cannot explain; I am astonished that they have not found an explanation for this. It has not yet been explained why this boy forgot his lightning calculations. It would be easy to say he wanted to forget them; that is the explanation given for so many lapses of memory. I agree with Dr. Putnam in one thing: The ability to calculate does not seem a feat of memory, particularly in the case described by Dr. Brill. It is puzzling to explain how the boy could add columns of five, six and seven digits in his mind. It is conducive to one's modesty to find that there are some things about which one really knows nothing.

DR. KURT GOLDSTEIN: Evidently in Dr. Brill's case the boy was a child of the type who have a special aptitude for numbers and who can handle them effectively without being able to use them with insight. There are various types of such children. Some have the capacity for handling numbers based on extraordinary visualization (so-called eidetic imagery). It has not been described clearly how the boy referred to by Dr. Brill proceeded in his additions. The fact that he executed them after having only heard the numbers, i. e., after verbal presentation, speaks for the possibility of an extraordinary auditory imagery.

Usually children with this ability are idiots, or at least are retarded in mental development. In cases in which there is only retardation of development, the children lose this special arithmetical capacity with further mental growth and increase in age. A boy whom I have studied personally during recent years has a special capacity for telling immediately the day of the week on which one was born if one gives him the date; further, he is able to retain these data for years. He is now 13 and cannot calculate with insight. His intelligence quotient is 50, and he cannot learn anything in school. Closer investigation has revealed that the capacity for abstraction has not developed in him. In such cases as Dr. Brill has presented the development of abstraction is only retarded. One cannot compare children of this type with mathematical prodigies. Mathematical prodigies do not lose their mathematical capacity; on the contrary, it grows with age. The phenomenon of an outstanding partial capacity appears in cases in which it is a symptom of mental defectiveness. In an earlier developmental stage it is difficult to predict whether the child will develop to normal mental capacity or not. Further investigations with regard to the capacity of abstraction—which usually begins

to appear in the fifth or sixth year—are necessary, as children who are impaired to a high degree in this respect will never develop normally, whereas children who show some degree of abstractability at this age will probably develop normally. It would be interesting to study the patient whom Dr. Brill has described at his present adult age; it may be that one could discover the reason for his ability to perform such difficult arithmetical tasks at an early age.

DR. A. A. BRILL: Dr. Jelliffe said that he is not a lightning calculator. From what I said, one can readily see why. Dr. Jelliffe, as every one knows and as he has just demonstrated, has an enormous amount of knowledge at his disposal. Almost all the youthful mathematicians who were able to absorb an education lost their talent for lightning calculation as soon as general knowledge was forced on them through schooling. The exceptions I mentioned or the persons who remained mathematicians showed direct hereditary influences in this direction, as in the case of the Bernoulli family.

As to the remarks made by Drs. Putnam, Goldstein and Sachs on the complexity of the phenomena: I believe that it is not as difficult as it sounds. When I first read Hering's vibration theory of memory I thought that it was fantastic, but the science of optics shows that any point of a medium through which a ray of light passes is affected by periodic movements, which occur regularly at equal intervals at no less than 5,000,000,000,000 vibrations per second, and that it is these movements which are conveyed to the optic nerves and cause one to see. What is even more remarkable is the fact that it is the difference in the rate of these movements which causes the diversity of color. Thus, one sees red when this movement occurs at a rate of 482,000,000,000,000 vibrations per second; one sees yellow when the movement occurs at a rate of 542,000,000,000,000, vibrations a second, and one sees violet when it occurs at a rate of 707,000,000,000,000 vibrations per second. This, too, sounds fantastic to those who have had little or no experience in the science of optics. My feeling is that there is something about memory which follows a certain rhythm, perhaps as divined by Hering, which is not as difficult as it seems. I believe all children possess such a rhythm or vibration, which they bring with them at birth, but that they lose it when they are placed in the artificial environment of civilization and are stuffed with all kinds of knowledge. It is not known whether animals possess this faculty, but they seem to calculate their lives in an almost perfect manner; e. g., birds and eels know when and where to migrate. In brief, I feel that this phenomenon is not as complex as it seems, that it more or less exists in every child, that it manifests itself in some and disappears later when artificially imposed knowledge crowds it out and that it remains only in those who cannot acquire new knowledge by virtue of their innate deficiency. I cannot explain it; I am too old and have not the technical knowledge for such investigation.

Book Reviews

Guiding Human Misfits: A Practical Application of Individual Psychology. By Alexandra Adler. Price, $1.75. Pp. 88. New York: The Macmillan Company, 1938.

This book follows closely the principles of individual approach formulated by Alfred Adler and enlarges on these principles in the light of the clinical experience of the author. The theme of the book is that, in order to understand the behavior of any individual person, it is necessary to know his "style of life," which is determined by his attempt at compensation or overcompensation for his shortcomings. Emphasis is placed on the importance of early childhood and the prevention rather than the cure of behavior and personality difficulties. It is the opinion of the author that children who are pampered or disliked or have organic inferiority are most likely to withdraw and become neurotic or to compensate by "bad" behavior.

Child guidance, neuroses, adolescence, the criminal, dreams and some practical aspects of child guidance and psychotherapy are discussed in a rather sketchy and superficial manner, with illustrative case material to add color. Because of the limited discussion and the strictly individual point of view, many readers will find this book inadequate as a dissertation on the mechanisms of human behavior. However, the book is written in terms understandable to the layman and deals with ways of behaving which are important to him.

The professional worker in the field of human behavior will find little of value in this book. The teacher, the student and the layman will find it useful as an introduction to the study of human relationships.

Der psychische Restitutionseffekt. O. Löwenstein. Price, 8 Swiss francs. Pp. 92, with 31 illustrations. Basel: Benno Schwabe & Co., 1937.

This study is a continuation of the author's work on the quantitative measurement of the pupillary reaction. By means of a refined apparatus he takes cinematographic pictures of the pupils under varying light conditions, with rigid control of other circumstances. If one eye is stimulated by exposure to light at regular intervals of from one to eleven seconds the pupillary reflex becomes fatigued. The more rapid the stimulation, the more rapid the fatigue. The fatigue is apparently of central origin, as it occurs even when the frequency of stimulation is extremely low. The intensity and duration of the stimulus seem to have little to do with the fatigue.

A remarkable circumstance is that the light reflex may become gradually or suddenly revived by psychic influences. Under these circumstances, all the steps of fatigue are retraced. The effective psychic influences may be either external or internal in origin. Repeated pleasurable stimulation is on the whole more effective than repeated unpleasant stimulation, which gradually loses its effect. The activity of the knee jerk shows a similar relationship to psychic influences.

The variability of physiologic response might be used to serve as an index of the extent of irrecoverable damage to the structures involved. This small monograph shows what interesting, and perhaps important, data may be elicited by intensive cultivation of a limited field.

CORRECTION

In the article entitled "Amyotrophic Lateral Sclerosis: Anatomic and Pathologic Considerations," by Dr. George B. Hassin, in the April issue (ARCH. NEUROL. & PSYCHIAT. **43**:765, 1940), the word "cerebral" in the second line of the legends for figures 4 and 5, on page 773, should read "cerebellar."